Exhibit 12
(Filed Under Seal)

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

IN RE NAMENDA DIRECT PURCHASER ANTITRUST LITIGATION	**No. 1:15-CV-07488-CM-JCF**

EXPERT REPORT OF GEORGE W. JOHNSTON, ESQ.

CONTAINS INFORMATION DESIGNATED "CONFIDENTIAL" OR "HIGHLY CONFIDENTIAL" UNDER THE PROTECTIVE ORDER

Table of Contents

Table of Contents (continued)

I. INTRODUCTION

1. I have been retained by counsel for Plaintiffs in the above-referenced matter to provide expert opinions regarding the matters set forth in this Report.

II. QUALIFICATIONS AND EXPERIENCE

2. I have been a patent attorney for over 40 years. I have extensive experience with patents, including evaluating the patentability of inventions, the scope of patent claims, the validity and enforceability of patents, and the infringement of patents. Moreover, I have drafted and successfully prosecuted hundreds of patent applications before the United States Patent and Trademark Office ("**USPTO**").

3. From 1977-2013, I was a member of the legal department of Hoffmann-La Roche Inc. ("**Roche**"), based in New Jersey, which is a U.S. affiliate of the Roche Group, a global pharmaceutical, biotechnology, and diagnostic health care organization headquartered in Basel, Switzerland.

4. My tenure at Roche included approximately seventeen years as Chief Patent Counsel. As a result of my experiences, I have participated in or supervised the prosecution of hundreds of U.S. patent applications before the USPTO concerning chemical, biotechnology, or pharmaceutical arts. I also have been directly involved with litigations associated with the resulting U.S. patents, including litigations brought under the *Drug Price Competition and Patent Term Restoration Act of 1984*[1] ("**Hatch-Waxman Act**").

5. Business units of Roche relied upon me and the members of the Roche patent department to determine the patent infringement risk associated with researching, developing, making, and selling pharmaceutical, biopharmaceutical, and diagnostic products, as well as vitamins, chemicals, and medical devices. For example, I would advise senior management on the likelihood that Roche would prevail in potential and actual patent litigations as a plaintiff or a defendant, the cost of the associated litigations, and the possible timing and duration of the litigations. I also provided advice on settling patent litigations, reducing legal risk, and strengthening the company's intellectual property rights.

6. In addition, I have been involved in the budgeting process for patent litigations, including Hatch-Waxman litigations. As Chief Patent Counsel for Roche, I advised senior management in establishing budgets and estimating the timing and duration for these litigations. I also interfaced with outside litigation counsel in reviewing litigation counsel's invoices in connection with these litigations.

[1] Pub. L. No 98-417, 98 Stat. 1585 (1984), and as amended.

7. My tenure at Roche also included approximately seven years as Vice President of Licensing. As a result, I have participated in or supervised hundreds of licensing negotiations and agreements concerning chemical, pharmaceutical, and biotechnology innovations.

8. The provisions of the Hatch-Waxman Act include aspects involving United States Food and Drug Administration ("**FDA**") law and U.S. patent law. While I do not practice in the area of FDA law, I have acquired some basic knowledge of this area of law based upon my experiences at Roche. I acquired this knowledge by having been a member of many cross functional drug development and drug approval teams during my tenure with Roche and through my experience with the Hatch-Waxman Act. Based upon my long-term involvement with intellectual property and the drug approval process, I served as a member of Roche cross-functional teams in the United States and globally that were involved with obtaining FDA approval for Roche drugs in development.

9. Throughout my career at Roche, my responsibilities also included, on behalf of Roche, listing and overseeing the listing of patents in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly called the "**Orange Book**") and consulting on the Hatch-Waxman Act. I was one of Roche's in-house attorneys who worked with the Pharmaceutical Manufacturers Association (formerly PMA, now PhRMA) during negotiations leading toward the enactment of the Hatch-Waxman Act. I also prepared and prosecuted patent term extension applications under 35 U.S.C. § 156 for Roche's marketed products.

10. In 2013, I retired from Roche as a Vice President and Chief Patent Counsel.

11. Later in 2013, I joined the law firm of Gibbons P.C. I am presently Counsel at Gibbons P.C. and practice intellectual property law.

12. A recent copy of my curriculum vitae ("**CV**") is attached as Exhibit A. My CV contains, among other things, a list of all publications I have authored in the previous ten years.

13. A more detailed discussion of my work history and experience is attached as Exhibit B.

III. MY ASSIGNMENT

14. Forest Laboratories, Inc. and Forest Laboratories Holdings, Ltd. (individually and collectively "**Forest**") and Merz Pharma GmbH & Co. KGaA, and Merz Pharmaceuticals GmbH (individually and collectively "**Merz**") brought suit against a number of generic companies, twelve of whom continued to litigate past the time to answer a complaint ("**Generic Companies**") alleging infringement of Merz's U.S. Patent No. 5,061,703 ("**'703 patent**") ("**Namenda Litigation**"). These Generic Companies attempted to obtain

FDA approval to market generic versions of Forest's Namenda® Tablets ("**Namenda**") before the expiration of the '703 patent.

15. For purposes of this Report, I have been asked to assess what a reasonable and competent patent attorney would have advised the litigants at the time they settled the Namenda Litigation in terms of (1) their likelihood of success in the litigation,[2] (2) each of the parties' likely litigation costs, and (3) the likely litigation timing, if the parties had not settled but rather had continued to litigate through a final, non-appealable judgment[3].

IV. SUMMARY OF MY OPINIONS

16. a. In my opinion, a reasonable and competent patent attorney[4] at the time of the settlement of the Namenda Litigation likely would have concluded that overall Mylan had greater than a 60% chance of prevailing and that Forest and Merz had less than A 40% chance of prevailing in the litigation through trial and appeal. In providing this opinion, I have taken a conservative approach in three regards:

- First, this was a case in which Mylan had a substantially better than 50-50 chance of success, particularly in view of the fact that it had raised a number of significant defenses, the success of any one of which would mean winning the litigation. Under these circumstances, a greater than 60% assessment of an overall likelihood of success is conservative;

- Second, viewing the historical statistics available to a reasonable and competent patent attorney at the time of the settlement, the lowest average likelihood of success percentage that could reasonably be attributed to an accused infringer was

[2] For clarity, I do not consider myself as a technical expert or a person of ordinary skill in the field of the '703 patent. I am not offering opinions in this Report that the asserted claims of the '703 patent are in fact valid or invalid, or infringed or not infringed. Likewise, I am not offering any scientific opinions from the vantage point of a person of ordinary skill. Instead, I am offering opinions as to the conclusions that a reasonable and competent patent attorney evaluating the evidence at the time of the Namenda Litigation settlement would reach based on his or her experience litigating and evaluating patent infringement cases as to: (1) the conclusions that a nontechnical court might likely reach regarding certain disputed factual and legal issues; and (2) the likelihoods of success of various invalidity and infringement defenses based on potential outcomes on disputed issues of law and fact.

[3] Forest and Merz settled with the Mylan in 2010. In offering these opinions, I have cited to and applied case law up to and including 2010 (unless otherwise noted), the year in which Forest/Merz and Mylan settled. I have also cited to and applied statutory law that was in effect at the time Forest and Merz filed complaints in the Namenda Litigation. Furthermore, for purposes of this Report I am relying on the Manual of Patent Examining Procedure ("**M.P.E.P.**") Eighth Edition, Revision 8 (July 2010), https://www.uspto.gov/web/offices/pac/mpep/old/mpep_E8R8.htm (last visited July 25, 2017).

[4] When referring to a "patent attorney" in the context of the likelihood of success in the Namenda Litigation, I mean a patent attorney with knowledge of patent litigation and at least 7 to 10 years of experience with patent litigation.

65%, and Mylan's case, based on my analysis of the merits, was in my opinion better than the average accused infringer's case; and

- Third, if a reasonable and competent patent attorney were to calculate Mylan's likelihood of success by calculating the likelihood that it would prevail on at least one case-dispositive defense (bearing in mind that Mylan needed to prevail only on any one of its invalidity or noninfringement defenses to win the case), then Mylan's overall chance of success would be significantly greater than 60%. And, thus, Forest and Merz's overall chance of success would be significantly less than 40%. *See* Section XII.

b. In addition and in my opinion, a reasonable and competent patent attorney at the time of the settlement of the Namenda Litigation likely would have concluded that Mylan had a 50% chance of prevailing on its patent term extension challenge, which if successful would have resulted in an expiration date for the '703 patent of September 12, 2013 or earlier. *See* Section XII.

17. In my opinion, a reasonable and competent patent attorney would have likely concluded that, absent settlement, the District Court would have entered final judgment in the Namenda Litigation between July 2010 and October 2010. If that judgment were appealed, a reasonable and competent patent attorney would have estimated that the Court of Appeals for the Federal Circuit ("**Federal Circuit**") would issue its appellate decision between about July 2011 and November 2011 (*i.e.*, approximately 15 to 19 months after the conclusion of the District Court trial), assuming no Rehearing. If a party then filed a petition for Rehearing, which was denied, and then filed a petition for certiorari to the Supreme Court of the United States ("**Supreme Court**"), which also was denied, a reasonable patent attorney would have estimated that the Federal Circuit decision would be made final between about January 2012 and June 2012 (*i.e.*, approximately 21 to 26 months after the conclusion of the District Court trial). *See* Section XIII.

18. In my opinion, a reasonable and competent patent attorney at the time of the settlement of the Namenda Litigation likely would have estimated Forest and Merz's costs savings for settling the Namenda Litigation with the last litigant, Mylan, to be about $3,500,000, if tried and appealed. In addition, a reasonable and competent patent attorney at the time of the settlement of the Namenda Litigation likely would have estimated Mylan's costs savings for settling the Namenda Litigation to be about $2,500,000 to $3,000,000, if tried and appealed. *See* Section XIV.

V. PATENTING PROCESS

19. A U.S. patent provides the patent holder with the right to seek to exclude others from making, using, selling, or importing the invention claimed in the patent for the period during which the patent is in force. 35 U.S.C. § 154.

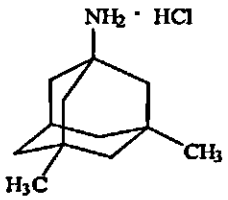
20. In Exhibit C, I describe the process for procuring a U.S. patent in the USPTO. I also set forth a procedure, called ex *parte* reexamination, for a patent owner or a third party to request that the USPTO reexamine an already-granted patent based on patents and printed publications that raise a substantial and new question of patentability.

21. Additionally, I discuss the process for extending the term of a pharmaceutical patent under the Hatch-Waxman Act. Finally, I describe the procedure under the Hatch-Waxman Act by which a generic manufacturer can challenge pharmaceutical patents listed in the Orange Book so it can enter the market before the patents expire.

VI. BACKGROUND – FACTUAL

A. Namenda ® Tablets (Package Insert)

22. Based upon the information as found in its Package Insert for Namenda[5] ("**Package Insert**"), Namenda (memantine HCl) is indicated for treatment of moderate to severe dementia of the Alzheimer's type. According to the Package Insert, "[m]emantine is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist which binds preferentially to the NMDA receptor-operated cation channels." Namenda's chemical name is 1-amino-3,5-dimethyladamantane hydrochloride. Namenda has the following chemical structure:



23. According to the Package Insert, Namenda tablets come in two forms containing either 5 mg or 10 mg of the active ingredient memantine hydrochloride[6]. Namenda tablets are

[5] Namenda (memantine HCl) [package insert]. Allergan, plc, 2013. https://www.allergan.com/assets/pdf/namenda_pi (last visited June 16, 2017).

[6] Based on the information in its package insert, Namenda is also available as an oral solution. Forest holds New Drug Application No. 21-627 on the Namenda oral solution (2 mg/ml). FDA, Drug Approval Package, Namenda Oral Solution, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021627s000_ NamendaTOC.cfm (last visited June 16, 2017).

capsule-shaped, film-coated, and tan (5 mg tablet) or gray (10 mg tablet). The strength (5 mg or 10 mg) is debossed on one side and FL is debossed on the other.

24. According to the Package Insert, the recommended starting dose of Namenda is 5 mg once daily. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice daily), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice daily). The minimum recommended interval between dose increases is one week. Based on the information as found in the Package Insert, the dose shown to be effective in controlled clinical trials is 20 mg/day. If a patient misses a single dose of Namenda, that patient should not double up on the next dose.

25. According to the Package Insert, the largest ingestion of memantine worldwide was 2.0 g in a patient who took memantine in conjunction with unspecified antidiabetic medications. The patient experienced coma, diplopia, and agitation, but subsequently recovered.

B. Forest's New Drug Application

26. Forest holds NDA No. 21-487 for Namenda 5 mg and 10 mg tablets. NDA No. 21-487 was approved by the FDA on October 16, 2003[7].

C. Forest's Orange Book Listing for Namenda

27. U.S. Patent No. 5,061,703 has been listed in the Orange Book for Namenda.

D. Abbreviated New Drug Applications for Generic Namenda Products

28. There are at least twenty-one (21) filed Abbreviated New Drug Applications ("**ANDAs**") for memantine hydrochloride 5mg/10mg tablets[8, 9].

---

[7] FDA, Drug Approval Package, Namenda (Memantine HCl) Tablets, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-487_Namenda.cfm (last visited June 16, 2017).

[8] FDA, Drugs@FDA: FDA Approved Drug Products, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (last visited June 16, 2017).

[9] Ajanta Pharma Ltd. holds ANDA No. 20-6528, which was approved on November 30, 2015. Alembic Pharmaceuticals Ltd. holds ANDA No. 20-0891, which was approved on October 13, 2015. Amneal Pharmaceuticals holds ANDA No. 09-0041, which was approved on April 10, 2015. Apotex Inc. holds ANDA No. 09-0244, which received tentative approval on May 1, 2012. Aurobindo Pharmaceuticals Ltd. holds ANDA No. 20-3175, which was approved on October 13, 2015. Dr. Reddy's Laboratories Ltd. holds ANDA No. 09-0048, which was submitted on October 16, 2007 and approved on April 14, 2010. Jubliant Generics holds ANDA No. 09-1585, which was approved on October 13, 2015. Lupin Ltd. holds ANDA No. 09-0051, which was submitted on October 16, 2007 and approved on April 10, 2015. MacLeods Pharmaceuticals Ltd. holds ANDA No. 20-2840, which was submitted on February 19, 2011 and approved on October 13, 2015. Mylan Pharmaceuticals Inc. holds ANDA No. 07-9225, which was approved on January 30, 2015. Orchid Healthcare holds ANDA No. 09-0044, which was

E. Merz's U.S. Patent No. 5,061,703 ('703 patent)

1. Filing Details

29. The '703 patent, entitled "Adamantane Derivatives in the Prevention and Treatment of Cerebral Ischemia," was filed in the United States on April 11, 1990 as U.S. Application Serial No. 07/508,109. The '703 patent issued on October 29, 1991. The '703 patent claims priority to E.P. Application No. 89106657, which was filed on April 14, 1989.

30. The named inventors of the '703 patent are listed as Joachim Bormann, Markus R. Gold, and Wolfgang Schatton. Merz + Co. CmbH & Co. is listed as the assignee on the '703 patent. Forest is the exclusive licensee of the '703 patent[10].

2. Alleged Inventive Concept

31. The '703 patent relates generally to methods for the treatment or prevention of cerebral ischemia using adamantane derivatives, including memantine and amantadine. The '703 patent recognizes that certain adamantane derivatives, including memantine, were already known and described in the art for the treatment of central nervous system disorders. *See* '703 patent, 1:41-42; 2:38-42 (referring to disubstituted aminoadamantanes (such as memantine) described in U.S. Patent No. 4,122,193 (issued on October 24, 1978)). The '703 patent specification discusses one mechanism of action of adamantane derivatives such as memantine through dopaminergic pathways, which compensates "the imbalance of the dopamine/acetylcholine system." *Id.* at 2:44-45.

32. The '703 patent then describes an alleged new mode of action of certain adamantane derivatives through NMDA receptor channels. In particular, the '703 patent identifies the "excessive inflow of calcium through NMDA receptor channels [which] finally leads to the destruction of brain cells in specific brain areas." *Id.* at 2:48-51. In fact, this is what named inventor, Dr. Bormann, described as the invention of the '703 patent:

---

submitted on October 16, 2007 and approved on March 12, 2012. Puracap Pharmaceuticals LLC holds ANDA No. 20-6855, which was approved on November 17, 2015. Silarx Pharmaceuticals Inc. holds ANDA No. 20-7236, which was approved on November 10, 2016. Strides Pharma holds ANDA No. 20-2350, which was approved on May 23, 2017. Sun Pharma Global holds ANDA No. 09-0058, which was approved on May 5, 2010. Teva Pharmaceuticals holds ANDA No. 09-0052, which was approved on October 25, 2011. Torrent Pharmaceuticals Ltd. holds ANDA No. 20-0155, which was approved on October 13, 2015. Unichem Laboratories Inc. holds ANDA No. 20-0022, which was approved on October 13, 2015. Upsher-Smith Laboratories holds ANDA No. 09-0043, which was submitted on October 16, 2007 and approved on July 31, 2015. Wockhardt Ltd holds ANDA No. 09-0073, which was submitted on October 11, 2007 and approved on September 4, 2015. Zydus Pharmaceuticals USA Inc. holds ANDA No. 09-0961, which received tentative approval on January 15, 2015.

[10] Proposed Joint Pretrial Order, *Forest Labs., Inc. v. Cobalt Labs. Inc.*, No. 08-21 (D. Del. Feb. 26, 2010) ("**Pretrial Order**"), MNAT_0000001-0000301, Exhibit 11, ¶ 25.

> [t]he invented concept is that neurodegeneration is caused by calcium overload of the cells and that you can prevent neurodegeneration by memantine or by adamantane derivatives. That's the invention.

(Bormann Dep. Transcript, *Forest Labs. Inc. v. Cobalt Labs. Inc.* (May 30, 2009) ("**Bormann Dep.**") 175:4–12.

33. The inventors, thus, considered the invention of the '703 patent as the discovery of a new mechanism of action of memantine and other adamantane derivatives (such as amantadine) on NMDA receptor channels.

34. The '703 patent describes several *in vitro* and *in vivo* experiments regarding NMDA receptor channels, including: A) displacement of TCP binding, an analogue to phencyclidine (PCP), a known NMDA receptor antagonist, '703 patent, 4:55-5:8; B) blocking of NMDA receptor channels in patch-clamp experiments, *id.* at 5:10-45; C) anti-convulsive effects of the adamantane derivatives, *id.* at 5:48-6:14; D) correlation between channel-blocking and anti-convulsive action, *id.* at 6:16-26; E) protection against cerebral ischemia in rats through occlusion of carotid arteries and treatment with adamantane derivatives, *id.* at 6:28-63; F) protection against NMDA-induced excitotoxicity in rats, *id.* at 6:64-7:20; and G) displacement binding studies of the adamantane derivatives in human brain slices. *Id.* at 7:23-62.

35. Although Examples 3 and 4, *id.* at 8:10-45 describe how to make tablets, there is no example in the '703 patent of the oral administration of memantine, or any other adamantane derivative, to a live human patient diagnosed with Alzheimer's disease.

F. Prosecution History of the '703 patent

36. Based on the information as found in its file history[11], the '703 patent was originally filed with 13 claims. Those claims encompassed methods for the prevention or treatment of cerebral ischemia comprising the step of administering to a patient in need thereof, an effective amount of an adamantane derivative, or a pharmaceutically-acceptable salt thereof. Claim 10 as originally filed was dependent upon claim 1 and was directed to the prevention or treatment of Alzheimer's disease.

37. In an Office Action dated January 15, 1991, the Examiner considered claims 1-9 and 11-13 to be allowable. Merz's pending claim 10, however, was rejected as lacking utility under 35 U.S.C. § 101, enablement under 35 U.S.C. § 112 and for obviousness under 35 U.S.C. § 103. The Examiner believed that "prevention" lacked utility and enablement. He

[11] https://portal.uspto.gov/pair/PublicPair (last visited July 17, 2017).

also believed that EP 0227410 disclosed the use of adamantane derivatives for the treatment of Alzheimer's disease.

38. Merz's attorney filed an Amendment on February 7, 1991 in response to the Office Action. In the Amendment, the word "prevention" in claim 10 was deleted. The attorney argued against the obviousness rejection by noting that "[t]here is absolutely nothing in [EP 0227410] which indicates that the adamantyl group has anything to do with the effectiveness of the compounds claimed in [EP 0227410] to be useful in the treatment of Alzheimer's disease or [Alzheimer's] dementia."

39. Merz's pending claim 10 was again rejected in a Final Office Action dated March 29, 1991. The Examiner rescinded the previous rejections and presented a new one under 35 U.S.C. § 112: that there was "insufficient exemplary support for 'treatment of Alzheimer's disease.'" Citing to a telephonic interview with Merz's attorney on March 26, 1991, the Examiner noted that an "agreement was not reached regarding claim 10 under 35 U.S.C. § 112, first paragraph." Merz replied to the Final Office Action in a Response dated May 20, 1991.

40. Merz's attorney argued that the finality of the Final Office Action was improper and asked for more time to respond to the new ground of the rejection. Merz's request however, was rendered moot because the USPTO mailed a Notice of Allowance on May 29, 1991, one week after receiving Merz's Response. No reasons for allowance were provided, and claims 1-13 issued on October 29, 1991. A copy of these 13 originally issued claims is attached as Exhibit F.

G. Reexamination of the '703 patent

41. Based on the information as found in Application No. 90/007,176[12], on August 18, 2004, 13 years after issuance of the '703 patent, Merz filed a request for reexamination of claims 1-3, 6, 8, and 10-12 of the '703 patent (Appl. No. 90/007,176).

42. Merz presented five prior art documents which it asserted as raising substantial new questions regarding patentability. On March 10, 2005, the USPTO presented four anticipation rejections under 35 U.S.C. § 102 against claims 1-3, 6, 8, and 10-12 as originally issued. In an Amendment dated May 9, 2005, Merz amended all of the issued claims to require "*orally* administering, to a patient *diagnosed with Alzheimer's disease.*" Merz further amended all the issued claims to exclude the administration of the adamantane derivative amantadine, and added new claims 14-19 which were also limited to "*orally* administering, to a patient *diagnosed with Alzheimer's disease*" adamantane derivatives, excluding adamantane. Merz also attempted to add new method claims 20-

[12] https://portal.uspto.gov/pair/PublicPair (last visited July 17, 2017).

25, which claimed a mechanism of action - *i.e.*, "a method of blocking an excessive influx of calcium through the NMDA receptor channels."

43. Merz filed two declarations in support of its above response. Merz used the declarations of Drs. Howard Fillit and Myron Weiner to amplify its argument of the alleged "surprising discovery" of administering memantine to Alzheimer's patients. Relying on those two declarations, Merz alleged that memantine in 1989 (*i.e.*, earliest foreign filing date) "was contraindicated for 'severe confusional states'" such as Alzheimer's disease and that it caused unwanted side effects such as agitation, which may have aggravated Alzheimer's symptoms. Merz also alleged that memantine was taught to be a dopaminergic agent in 1989, but that treatment of Alzheimer's disease in 1989 was focused on the cholinergic system instead. Merz concluded that a skilled artisan would, therefore, not have turned to memantine for the treatment of Alzheimer's disease.

44. Among other rejections, Merz's claim 10 was rejected in a Final Office Action dated August 16, 2005, as being indefinite under 35 U.S.C §112 for not further limiting independent claim 1 from which it depends. Newly added mechanism of action claims 20-25 were rejected under 35 U.S.C. § 305 as enlarging the scope of the claims during reexamination.

45. In an Amendment dated October 17, 2005, Merz amended dependent claim 10 to recite that the "effective amount" of memantine administered was "from about 0.01 to 100 mg/kg." Merz also cancelled mechanism of action claims 20-25, citing to an agreement reached with the Examiner during a September 26, 2005 telephonic interview. The cancellation of claims 20-25 rendered the Examiner's broadening claim rejection moot.

46. On November 7, 2006, the USPTO issued an *Ex Parte* Reexamination Certificate for the '703 patent, amending independent claim 1 and dependent claim 10, and adding new claims 14-19. A Certificate of Correction was subsequently issued for the '703 patent on June 5, 2007. A copy of all the claims of the '703 patent remaining after reexamination is attached as Exhibit G.

H. Patent Term Extension Application for the '703 patent

47. The original expiration date of the '703 patent was April 11, 2010. On December 9, 2003, Forest filed a Request for Extension of Patent Term under 35 U.S.C. § 156 for the '703 patent ("**PTE Application**") based upon the FDA's approval of the product Namenda (NDA No. 21-487). Forest requested the USPTO extend the term of the '703 patent by 1,250 days (approximately 3.4 years).

48. As required in a PTE Application, Forest provided a brief description of the significant activities it undertook during the applicable regulatory review period with respect to

Namenda and the significant dates applicable to such activities. A chronology of the prosecution of the PTE Application of the '703 patent is set forth in Exhibit H.

49. Also, as required in a PTE Application, Forest provided specific dates for the testing phase[13] and the approval phase[14] of the regulatory review period[15] for Namenda[16]. In particular, Forest indicated that the testing phase started on October 9, 1997 (*i.e.*, the date the IND became effective). Later, the HHS Secretary determined that this date was incorrect.

50. In a letter dated May 16, 2007, the Secretary of Health and Human Services ("**HHS Secretary**") notified the USPTO that it had determined the regulatory review period for Namenda. Regarding the start of the testing phase of the regulatory review period, the HHS Secretary concluded that according to FDA's records, the IND for Namenda had an effective date of February 7, 1990, rather than October 9, 1997. Thus, the HHS Secretary expanded the testing phase to include the time between February 7, 1990 and October 9, 1997.

51. Based on the regulatory review period as determined by the HHS Secretary, the USPTO calculated the patent term extension to be 5 years (approximately 1,826 days). In particular, the USPTO subtracted 630 days from the 4,699 days of the testing phase, representing the portion of the regulatory review period that occurred up to the date on which the '703 patent issued (October 29, 1991). Applying the formula that "Period of Extension = ½(testing phase) + approval phase," the USPTO calculated that the period of extension for the '703 patent was 2,336 days, which it then limited to 5 years under 35 U.S.C. § 156(g)(6)(A).

52. When calculating the Patent Term Extension for Namenda, the USPTO did not subtract any days for lack of due diligence. As noted above, Forest did not amend its PTE Application to address whether there was continuous due diligence within the expanded testing phase (*i.e.*, between February 7, 1990 and October 9, 1997)[17].

---

[13] The testing phase for a human drug product is the period between the effective date of an investigational product exemption (Investigational New Drug Application or "**IND**") and the initial submission of the marketing application (New Drug Application or "**NDA**").

[14] The approval phase for a human drug product is the period between the date on which a NDA was initially submitted, and the date on which the NDA was approved.

[15] The "regulatory review period" comprises two parts: a **testing phase** and an **approval phase**.

[16] In particular, Forest provided the effective date of the IND (*i.e.*, February 7, 1990), the date on which a NDA was initially submitted (*i.e.*, October 9, 1997), and the date on which the NDA was approved (*i.e.*, October 16, 2003).

[17] In other words, in its PTE Application at p. 14, Forest provided the number of days within the testing phase and approval phase during which the applicant asserted "failed to act with due diligence" during that phase. The number

53. On March 18, 2009, the USPTO issued a Certificate Extending Patent Term under 35 U.S.C. § 156 for the '703 patent, extending the term of the '703 Patent for a period of 5 years, until April 11, 2015.

54. In the PTE Application at p. 15, Forest acknowledged its duty to disclose to the Commissioner of Patents and Trademarks and to the HHS Secretary any information which is material to the determination of entitlement to the extension sought for the '703 patent, as required by 37 C.F.R. § 1.765 ("**duty of disclosure**").

I. Foreign Prosecution of Patents corresponding to the '703 patent

55. Foreign counterparts of the '703 patent have been revoked in Germany and Canada[18]. In Germany, EP 0392059 (DE 58905637) was invalidated as lacking novelty and inventive stepover several prior art articles, including Fleischhacker *et al.*, Prog. Neuro-Psychopharmacol. & Biol. Psychiatry, 10:87-93 (1986). Bundespatentgericht [Federal Patent Court] December 11, 2007, 3 Ni 59/05 (EU) BPatG 253 (F.R.G.). In Canada, CP 2,014,453 was invalidated as anticipated over the following references: 1) Rote Liste (1986); 2) Ambrozi & Danielczyk, Pharmacopsychiatry 21:144-46 (1988); and 3) Japanese Patent No. 58-4718 (1983) ("Ishizu Application"); and, as obvious over those same references as well as 1) Marcea et al., Therapiewoche 38:3097-3100 (1988) and 2) Fleischhacker et al., Prog. Neuro Psychopharmacol. & Biol. Psychiatry, 10:87-93 (1986). Lundbeck Canada Inc. v. Ratiopharm Inc., 2009 FC 1102 (Fed. Ct. November 23, 2009) (Can.).

---

applicant provided for each phase was zero. Forest never updated this number to take into consideration the additional time within the expanded testing phase.

[18] Although not precisely the same, "novelty" is generally considered the foreign equivalent of "anticipation' under 35 U.S.C §102. *See* Canadian Patent Office Manual of Patent Office Practice, § 15.01 (2017) (stating "[i]n order for an invention to be novel, it must be established that the individual disclosures in the prior art do not anticipate the claimed invention"); *see also* Guidelines for Examination in the European Patent Office, Part G, VI.1 (2016) (stating "[a]n invention is considered to be new if it does not form part of the state of the art" and that "in considering novelty . . . it is not permissible to combine separate items of prior art together"). The Canadian Patent Office Manual of Patent Office Practice further provides that "[a]nticipation is assessed on a claim-by-claim basis by asking whether the prior disclosure, when understood by a person skilled in the art in light of their common general knowledge, provides both a description of the claimed invention (disclosure) and sufficient instructions to enable the invention to be practised [sic] (enablement)" and that "[a] prior disclosure is considered to be enabling for the purpose of anticipation if the person skilled in the art, where necessary through trial and error experimentation that is neither inventive nor an undue burden, can operate the disclosed invention successfully." Canadian Patent Office Manual of Patent Office Practice, § 15.01 (2017). Likewise, "inventive step" is generally considered the foreign counterpart of "obviousness" under 35 U.S.C §103. *See* Canadian Patent Office Manual of Patent Office Practice, § 16.07 (2017) (stating, "[a] claimed invention must be the result of ingenuity, and a conclusion of obviousness is equivalent to a conclusion of lack of inventive step"); *see also* Guidelines for Examination in the European Patent Office, Part G, VII.1 (2016) (stating "[a]n invention is considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the Art").

56. A translation of the claims revoked in Germany and copy of the claims revoked in Canada are attached as Exhibit I.

VII. PARAGRAPH IV NOTICE LETTERS REGARDING THE '703 PATENT

A. Generic Companies

57. Forest and Merz alleged that they received Paragraph IV Certification Notices ("**Notice Letters**") from the following 15 generic companies: TEVA Pharmaceuticals USA Inc. on or about November 30, 2007; Cobalt Labs, Inc. on or about December 6, 2007; Barr Laboratories Inc. on or about December 10, 2007; Orchid Healthcare on or about December 11, 2007; Lupin Pharma and Upsher-Smith Laboratories on or about December 14, 2007; Wockhardt USA on or about December 15, 2007; Genpharm LP and Mylan Pharmaceuticals Inc. on or about December 18, 2007; Interpharm Inc. and Ranbaxy on or about December 19, 2007; Sun India Pharmaceutical Industries Limited on or about December 20, 2007; Dr. Reddy's Limited on or about January 4, 2008; Synthon Labs on or about February 5, 2008; and Apotex on or about April 23, 2008[19].

B. Defenses Raised in the Notice Letters

58. In their Notice Letters, the Generic Companies argued a variety of defenses including noninfringement and invalidity of the '703 patent under 35 U.S.C. §§ 101, 102, 103, 112, 156, and 305[20]. A summary of the various defenses are found on Exhibit J.

---

[19] Complaint, *Forest Labs., Inc. v. Cobalt Labs. Inc.*, No. 08-21 (D. Del. Jan. 10, 2008), ECF No. 1; *see also* Amended Complaint, *Forest Labs., v. PLIVA D.D.*, No. 08-22 (D. Del. Jan 17, 2008), ECF No. 11; *see also* Amended Complaint, *Forest Labs., Inc. v. Dr. Reddy's Labs., Inc.*, No. 08-52 (D. Del. Feb. 15, 2008), ECF No. 31; *see also* Complaint, *Forest Labs., Inc. v. Orgenus Pharma Inc.*, No. 08-291 (D. Del. May 16, 2008), ECF No. 1; *see also* Complaint, *Forest Labs., Inc. v. Apotex Inc.*, No. 08-336 (D. Del. June 5, 2008), ECF No. 1.

[20] FRX-AT-03490244-277 (Cobalt Labs, Inc.'s Notice Letter); *see also* FRX-AT-03490110-131 (Lupin Pharma's Notice Letter); *see also* FRX-AT-03488151-168 (TEVA Pharmaceuticals USA Inc.'s Notice Letter); *see also* FRX-AT-03169274-299 (Upsher-Smith Laboratories' Notice Letter); *see also* FRX-AT-03490173-243 (Wockhardt USA's Notice Letter); *see also* FRX-AT-02588339-346 (Barr Laboratories Inc.'s Notice Letter); *see also* FRX-AT-03490041-068 (Dr. Reddy's Limited's Notice Letter); *see also* FRX-AT-03490069-109 (Genpharm LP's Notice Letter); *see also* FRX-AT-03490296-318 (Interpharm Inc.'s Notice Letter); *see also* FRX-AT-03490132-172 (Mylan Pharmaceuticals Inc.'s Notice Letter); *see also* FRX-AT-03169490-503 (Sun India's Notice Letter); *see also* FRX-AT-03169532-547 (Synthon's Notice Letter); *see also* FRX-AT-03169548-561 (Apotex's Notice Letter); *see also* FRX-AT-03483932-947 (Ranbaxy Laboratories Ltd.'s Notice Letter); *see also* FRX-AT-03169232-273 (Orchid Healthcare's Notice Letter).

VIII. HISTORY OF THE '703 PATENT LITIGATIONS AGAINST THE GENERIC COMPANIES

A. Procedural History

59. In response to the above Notice Letters, Forest and Merz instituted a number of Hatch-Waxman litigations in the United States District Court for the District of Delaware[21, 22] and elsewhere[23].

60. Thus, PACER[24] reveals that Forest and Merz sued the following generic companies in the District of Delaware: Cobalt, Lupin, Teva, Upsher-Smith, Wockhardt, Barr, Dr. Reddy's,

---

[21] In the United States District Court for the District of Delaware, Forest and Merz filed a complaint on January 10, 2008 in Case No. 08-21 against Cobalt Laboratories Inc. (hereinafter, "**Cobalt**"), Lupin Pharmaceuticals, Inc. and Lupin Ltd. (collectively "**Lupin**"), Orchid Chemicals & Pharmaceuticals Ltd. (d/b/a Orchid Healthcare) (hereinafter, "**Orchid**"), Teva Pharmaceuticals USA, Inc. (hereinafter, "**Teva**"), Upsher-Smith Laboratories, Inc. (hereinafter, "**Upsher-Smith**"), Wockhardt USA, Inc. and Wockhardt Limited (collectively, "**Wockhardt**"); filed a complaint on January 10, 2008 in Case No. 08-22 against Barr Laboratories, Inc. and Barr Pharmaceuticals, Inc., which was amended on January 17, 2008 to add PLIVA d.d. and PLIVA-Hrvatska d.o.o. (collectively, "**Barr**"); filed a complaint on January 25, 2008 in Case No. 08-52 against Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories Ltd. (collectively, "**Dr. Reddy's**"); Genpharm Inc. and Genpharm, L.P. (collectively, "**Genpharm**"); Interpharm Holdings, Inc. and Interpharm, Inc. (collectively, "**Interpharm**"); Mylan Pharmaceuticals Inc. (hereinafter, "**Mylan**"); Ranbaxy Inc. and Ranbaxy Laboratories Limited (collectively, "**Ranbaxy**"); Kendle International Inc. (hereinafter, "**Kendle**"); and Sun India Pharmaceutical Industries Limited (a/k/a Sun Pharmaceutical Industries Limited) (hereinafter, "**Sun**"), which was amended on February 15, 2008 to add Synthon holding B.V., Synthon B.V., Synthon Laboratories, Inc., and Synthon Pharmaceuticals, Inc. (collectively, "**Synthon**"); filed a complaint on May 16, 2008 in Case No. 08-291 against Orgenus Pharma Inc. (hereinafter, "**Orgenus**"); and filed a complaint on June 5, 2008 in Case No. 08-336 against Apotex Inc. and Apotex Corp. (collectively, "**Apotex**").

[22] Unless otherwise noted, each ECF Docket Entry Number ("ECF No.") refers to the docket in *Forest Labs Inc. v. Cobalt Labs Inc.*, Case No. 08-21, D. Del.

[23] Additionally, Forest and Merz initiated related Hatch-Waxman litigations in a number of other federal district courts. Forest and Merz filed complaints against: Upsher-Smith in the District of Minnesota on January 28, 2008 (Case No. 08-253); Lupin in the District of Maryland on January 28, 2008 (Case No. 08-239); Mylan in the Northern District of West Virginia on January 31, 2008 (Case No. 08-73); Genpharm in the Eastern District of New York on January 31, 2008 (Case No. 08-444); Kendle in the Southern District of Ohio on February 4, 2008 (Case No. 08-78); Sun in the Northern District of Illinois on February 4, 2008 (Case No. 08-749); and Synthon in the Eastern District of North Carolina on March 20, 2008 (Case No. 08-150). Forest also filed an action against Aurobindo Pharma USA Inc. and Aurobindo Pharma Ltd. in the District of Delaware on June 27, 2014 (Case No. 14-833). Each of the aforementioned matters was terminated by voluntary dismissal by Forest and Merz before any of the generic company defendants answered. Notice of Voluntary Dismissal, *Forest Labs, Inc. v. Upsher-Smith Labs, Inc.* No. 08-253 (D. Minn. Feb. 5, 2008), ECF No. 6; *see also* Order Approving Notice of Voluntary Dismissal, *Forest Labs, Inc. v. Lupin Pharma Inc.*, No. 08-239 (D. Md. Feb. 6, 2008), ECF No. 9; *see also* Notice of Voluntary Dismissal, *Forest Labs, Inc. v. Mylan Pharma Inc.*, No. 08-73 (N.D. W. Va. Feb. 20, 2008), ECF No. 8; *see also* Notice of Voluntary Dismissal, *Forest Labs, Inc. v. Genpharm, L.P.*, No. 08-444 (E.D.N.Y. Mar. 3, 2008), ECF No. 9; *see also* Notice of Voluntary Dismissal, *Forest Labs, Inc. v. Kendle Int'l Inc.*, No. 08-78 (S.D. Ohio Feb. 28, 2008), ECF No. 9; *see also* Minute Entry Dismissing Case, *Forest Labs, Inc. v. Sun India Pharma. Indus. Ltd.*, No. 08-749 (N.D. Ill. Mar. 4, 2008), ECF No. 11; *see also* Notice of Voluntary Dismissal, *Forest Labs, Inc. v. Synthon Pharma. Inc.*, No. 08-150 (E.D.N.C. May 22, 2008), ECF No. 15; *see also* So Ordered as to Stipulation of Dismissal, *Forest Labs, Inc. v. Aurobindo Pharma USA Inc.*, No. 14-833, (D. Del. Nov. 14, 2014).

Genpharm, Amneal[25], Mylan, Ranbaxy[26], Kendle[27], Sun, Synthon[28], Orchid, Orgenus[29], and Apotex. Twelve of these defendants[30] remained in the Namenda Litigation beyond the time for filing an answer. Moreover, the earliest suit was filed by Forest and Merz on January 10, 2008. *See* Report, Footnote 21.

61. On June 2, 2008, Case Numbers 08-22, 08-52, and 08-291 in the District of Delaware were consolidated into Case Number 08-21[31]. On June 16, 2008, Case Number 08-336 was also consolidated into Case No. 08-21[32] (all collectively, "**Namenda Litigation**").

62. Claims 1-3, 6, 8, 10-12, and 14-19 of the '703 patent were at issue in the Namenda Litigation.

---

[24] Public Access to Electronic Court Records, https://pacer.login.uscourts.gov/csologin/login.jsf?appurl=pcl.uscourts.gov/search.

[25] Amneal Pharmaceuticals of New York, LLC and Amneal Pharmaceuticals, LLC (hereinafter, "**Amneal**") (as successors in interest to Interpharm) answered Forest and Merz's complaint against Interpharm. *See* Amneal's Amended Answer and Counterclaims, ECF No. 327. Hereinafter for clarity, I refer to Amneal rather than to Interpharm.

[26] Ranbaxy was dismissed via consent judgment before filing an answer. Consent Judgment, *Forest Labs. Inc. v. Dr. Reddy's Labs. Inc.*, No. 08-52 (D. Del. Apr. 14, 2008), ECF No. 78.

[27] Kendle was dismissed before filing an answer. Notice of Voluntary Dismissal, *Forest Labs. Inc. v. Dr. Reddy's Labs, Inc.*, No. 08-52 (D. Del. Feb. 28, 2008), ECF No. 42.

[28]Synthon was dismissed via stipulation before filing an answer upon withdrawal of its ANDA. Stipulation and Order of Dismissal, *Forest Labs. Inc. v. Dr. Reddy's Labs. Inc.*, No. 08-52 (D. Del. May 16, 2008), ECF No. 87; *see also* So-Ordered re: Stipulation and Order of Dismissal, *Forest Labs. Inc. v. Dr. Reddy's Labs. Inc.*, No. 08-52 (D. Del. May 19, 2008).

[29] On August 27, 2009, the cases against Orgenus and Orchid were transferred to the United States District Court for the District of New Jersey. Memorandum and Order, ECF No. 407. In the New Jersey matter, Orgenus and Orchid filed answers, Orchid's Answer and Counterclaim, *Forest Labs Inc. v. Orgenus Pharma. Inc.*, No. 09-5105, (D.N.J. Oct. 14, 2009), ECF No. 5; *see also id.* at Orgenus' Answer and Counterclaim, Oct. 14, 2009, ECF No. 6, and Forest and Merz filed answers to the counterclaims. *Id.* at Answer to Counterclaim, Dec. 31, 2009, ECF No. 15; *see also id.* at Answer to Counterclaim, Dec. 31, 2009, ECF No. 16. Forest and Merz, however, voluntarily dismissed that case before an initial scheduling conference was held. *Id.* at Stipulation and Order Dismissing the Case, Apr. 26, 2010, ECF No. 26.

[30] That is, Cobalt, Lupin, Teva, Upsher-Smith, Wockhardt, Barr, Dr. Reddy's, Genpharm, Amneal, Mylan, Sun, and Apotex.

[31] Order of Consolidation, ECF No. 76. The Consolidation Order provided that Case Nos. 08-21, 08-22, 08-52, and 08-291 "are consolidated for all purposes." *Id.*

[32] Order of Consolidation, ECF No. 83. The Consolidation Order provided that Case No. 08-336 was consolidated with Case No. 08-21 "for all purposes." *Id.*

B. Defenses Alleged During the Namenda Litigation

63. In their Answers and Counterclaims in the Namenda Litigation, the Generic Companies asserted a number of defenses including: noninfringement; invalidity under 35 U.S.C. §§ 101, 102, 103, 112 and 305; failure to state a claim; lack of subject matter jurisdiction; unclean hands; prosecution history estoppel; inequitable conduct; failure to comply with 35 U.S.C. § 156; patent misuse; equitable intervening rights; as well as counterclaims seeking: declaratory judgment of noninfringement and invalidity; an order to de-list the '703 patent from the Orange Book; and a declaratory judgment of invalidity of the patent term extension of the '703 patent[33].

C. *Markman* Claim Construction

64. The parties engaged in claim construction briefing[34]. A Technology Tutorial was provided to the Court on November 12, 2008[35]. On July 2, 2009, the Magistrate Judge issued a Report and Recommendation Regarding Claim Construction. *Forest Labs. Inc. v. Cobalt Labs. Inc.*, No. 08-21, 2009 WL 1916935 (D. Del. July 2, 2009).

65. Thereafter, four groups of Generic Companies filed objections to the Magistrate Judge's Report and Recommendation. On September 21, 2009, the District Judge entered an order adopting in part and overruling in part, the Magistrate Judge's Report and Recommendation. *Forest Labs. Inc. v. Cobalt Labs. Inc.*, No. 08-21, 2009 WL 3010837 (D. Del. Sept. 21, 2009). The District Judge addressed only the construction of those terms to which the Generic Companies objected and adopted the Magistrate Judge's construction of the remaining terms. *See generally id.* at *1–3.

---

[33] Sun's Amended Answer and Counterclaims, ECF No. 217-2; *see also* Mylan's Second Amended Answer, ECF No. 322; *see also* Genpharm's Second Amended Answer and Counterclaims, ECF No. 323; *see also* Orchid's Amended Answer, ECF No. 324; *see also* Apotex's Second Amended Answer and Counterclaims, ECF No. 325; *see also* Teva's Second Amended Answer, ECF No. 326; *see also* Amneal's Amended Answer and Counterclaims, ECF No. 327; *see also* Dr. Reddy's Amended Answer and Counterclaims, ECF No. 328; *see also* Cobalt's Second Amended Answer and Counterclaims, ECF No. 330; *see also* Upsher-Smith's Amended Answer, ECF No. 331; *see also* Wockhardt's Amended Answer and Counterclaims, ECF No. 335; *see also* Lupin's Amended Answer and Counterclaims, ECF No. 406; *see also* PLIVA-Hrvatska d.o.o, Barr Labs. Inc. and Barr Pharma. Inc.'s Answer to Amended Complaint and Counterclaims, *Forest Labs. Inc. v. Barr Labs. Inc.*, No. 08-22 (D. Del. Mar. 3, 2008), ECF No. 18; *see also* PLIVA d.d.'s Answer to Amended Complaint, *Forest Labs. Inc. v. Barr Labs. Inc.*, No. 08-22 (D. Del. Mar. 3, 2008), ECF No. 19.

[34] On October 17, 2008, the parties filed a Joint Claim Chart (Claim Construction Chart, ECF No. 198), on Nov. 7, 2008, the parties filed their opening claim construction briefs – with Generic Companies filing jointly one brief, Generic Companies' Joint Opening Claim Construction Brief, ECF No. 222; *see also* Plaintiffs' Opening Claim Construction Brief, ECF No. 223, and on November 24, 2008, the parties filed their answering claim construction briefs – again with Generic Companies filing jointly one brief. Plaintiffs' Claim Construction Answering Brief, ECF No. 235; *see also* Generic Companies' Joint Claim Construction Answering Brief, ECF No. 236. On December 15, 2008, the Magistrate Judge held a *Markman* hearing. Hearing Transcript, ECF No. 248.

[35] Transcript of Oral Argument/Technology Tutorial, ECF No. 226; *see also* Minute Entry, Nov. 12, 2008.

66. Specifically, the District Judge considered the terms: (1) "cerebral ischemia"; (2) "prevention of cerebral ischemia" and "treatment of cerebral ischemia"; (3) "Treatment of imbalance of neuronal stimulation after Alzheimer's disease"; and (4) "Treatment of Alzheimer's Disease." *Id.* The District Judge adopted the Magistrate Judge's construction for each of those disputed terms except for "Treatment of imbalance of neuronal stimulation after Alzheimer's disease" and "Treatment of Alzheimer's disease." *Id.*

67. The District Judge construed "Treatment of imbalance of neuronal stimulation after Alzheimer's disease," to mean "an antagonistic intervention with regard to the excessive inflow of calcium through NMDA receptor channels after Alzheimer's disease" based on a perceived "clerical error or other inadvertent oversight" by the Magistrate Judge with respect to the phrase "after Alzheimer's disease." *Id.* at *2. The District Judge construed "Treatment of Alzheimer's disease," in claim 10 to have "it's plain and ordinary meaning," *id.* at *3, and further ordered that the construction "incorporated by inference the court's construction of 'Alzheimer's disease.'" *Id.* at *4 n.1. In so finding, the District Judge reasoned that "[i]t seems clear from the post-reexamination claims that the distinction between claim 1 and claim 10 lies not in the persons receiving the treatment, but rather in the characteristics of the adamantane derivative described." *Id.*

68. The results of the Court's *Markman* Claim Construction are summarized in a table attached in Exhibit K.

D. Settlement of Namenda Litigation (circa 2009–2010)

69. At various points throughout the Namenda Litigation, stipulations of dismissal were filed until each Generic Company was dismissed. The docket reveals that consent judgments, dismissal and stay stipulations were filed on the following dates[36]:

[36] On May 8, 2009 after the *Markman* hearing, but before the Magistrate Judge's Report and Recommendation, a stipulation of dismissal as to Barr was filed and Barr was dismissed from the action on May 11, 2009. Stipulation of Dismissal as to Barr, ECF No. 329; *see also* So-Ordered as to ECF No. 329 (dismissing Barr). Between September 2 and September 10, 2008 after the Magistrate Judge's *Markman* Report and Recommendation, but before the District Judge's *Markman* Opinion and Order, stipulations of dismissal were filed as to Upsher-Smith, Apotex, Amneal, and Wockhardt and on September 11, 2009 those Generic Companies were dismissed from the action. Stipulation of Dismissal as to Amneal, ECF No. 409; *see also* So-Ordered, ECF No. 418 (dismissing Amneal); *see also* Stipulation of Dismissal as to Upsher-Smith, ECF No. 412; *see also* So-Ordered, ECF No. 416 (dismissing Upsher-Smith); *see also* Stipulation of Dismissal as to Apotex, ECF No. 413; *see also* So-Ordered, ECF No. 417 (dismissing Apotex); *see also* Stipulation of Dismissal as to Wockhardt, ECF No. 415; see *also* So-Ordered, ECF No. 419 (dismissing Wockhardt). On October 8, 2009, after the District Judge's *Markman* Opinion and Order, a stipulation of dismissal was filed as to Genpharm and on October 14, 2009, Genpharm was dismissed from the action. Stipulation as to Genpharm, ECF No. 432; *see also* So-Ordered, Oct. 14, 2009 (dismissing Genpharm). On October 9, 2009, a stipulation of dismissal was filed as to Sun and on October 15, 2009, Sun was dismissed from the action. Stipulation as to Sun, ECF No. 432; *see also* So Ordered, ECF No. 434 (dismissing Sun). On October 19, 2009, a stipulation of dismissal as to Cobalt was filed and on October 20, 2009, Cobalt was dismissed from the action. Stipulation as to Cobalt, ECF No. 437; *see also* So Ordered, ECF No. 439 (dismissing Cobalt). On November 5, 2009, a stipulation of dismissal as to Teva was filed and on November 10, 2009, Teva was dismissed

Table - Namenda Litigation – Consent Judgments, Dismissals and Stays

Date	Event
February 28, 2008	Stipulation of Dismissal as to Kendle
April 10, 2008	Consent Judgment of Ranbaxy
May 16, 2008	Stipulation of Dismissal as to Synthon
May 8, 2009	Stipulation of Dismissal as to Barr
September 2, 2009	Stipulation of Dismissal as Amneal
September 8, 2009	Stipulation of Dismissal as to Upsher-Smith
September 9, 2009	Stipulation of Dismissal as to Apotex
September 10, 2009	Stipulation of Dismissal as to Wockhardt
October 8, 2009	Stipulation of Dismissal as to Genpharm
October 9, 2009	Stipulation of Dismissal as to Sun
October 19, 2009	Stipulation of Dismissal as to Cobalt
November 5, 2009	Stipulation of Dismissal as to Teva
November 16, 2009	Stipulation to Stay as to Dr. Reddy
December 14, 2009	Stipulation of Dismissal as to Dr. Reddy
December 14, 2009	Stipulation to Stay as to Lupin
February 11, 2010	Stipulation of Dismissal as to Lupin
July 22, 2010	Stipulation to Stay as to Mylan
August 26, 2010	Stipulation of Dismissal as to Mylan

E. Namenda Litigation Against Mylan

70. Mylan's case progressed the farthest[37]. The docket reveals that Forest and Merz, and Mylan completed factual and expert discovery and filed a joint proposed pretrial order[38]. A one week trial was scheduled for April 5, 2010.

---

from the action. Stipulation as to Teva, ECF No. 450; *see also* So Ordered, ECF No. 452 (dismissing Teva). On November 16, 2009, a stipulation to stay as to Dr. Reddy's was filed; on December 14, 2009, a stipulation of dismissal was filed as to Dr. Reddy's; and on December 29, 2009, Dr. Reddy's was dismissed from the action. Stipulation to Stay as to Dr. Reddy's, ECF No. 453; *see also* Stipulation as to Dr. Reddy's, ECF No. 458; *see also* So Ordered, ECF No. 464 (dismissing Dr. Reddy's). On July 22, 2010, a stipulation to stay as to Mylan was filed, on August 26, 2010 a stipulation to stay as to Mylan was filed, and on September 1, 2010, Mylan was dismissed from the action. Stipulation to Stay, ECF No. 496; *see also* Stipulation as to Mylan, ECF No. 498; *see also* So Ordered, ECF No. 500 (dismissing Mylan). On February 11, 2009, a stipulation of dismissal was filed as to Lupin and on September 27, 2010, Lupin was dismissed from the action. Stipulation of Dismissal as to Lupin, ECF No. 466; *see also* So Ordered, ECF No. 502.

[37] Although Lupin was the last Generic Company dismissed from the action, a stipulation of dismissal as to Lupin was filed by the parties on February 11, 2010 (Stipulation of Dismissal, Feb. 11, 2010, ECF No. 466), more than seven months before the District Court entered the order dismissing Lupin. Letter, Aug. 26, 2010, ECF No. 499 (advising that the matter had been settled with respect to Mylan and that a stipulation had been filed with respect to Lupin in February).

[38] Order Amending Scheduling Order, July 20, 2009, ECF No. 380 (setting an Oct. 2, 2009 fact discovery deadline, a Dec. 23, 2009 expert discovery deadline, and providing that "motions for summary judgment will not be permitted"); *see also* Pretrial Order, ECF No. 468.

71. After the pretrial order was filed on February 26, 2010, a pretrial conference was scheduled for March 16, 2010. Oral Order Scheduling Pretrial Conference, Mar. 10, 2010. On March 16, 2010, Mylan's counsel wrote to the District Court advising that the parties had reached an agreement-in-principle on March 15, 2010. Letter, ECF No. 478. On July 22, 2010, the parties filed a stipulation to stay the litigation as to Mylan "in view of the parties' settlement negotiations," Stipulation and Order, ECF No. 497, and the District Court ordered the stay on July 27, 2010. So Ordered re: Stipulation to Stay, ECF No. 498. On August 26, 2010, a stipulation of dismissal as to Mylan was filed, *see* Stipulation of Dismissal, ECF No. 498, and on September 1, 2009, the District Court so ordered the stipulation, dismissing Mylan from the Namenda Litigation. So Ordered re: Stipulation of Dismissal, ECF No. 500.

72. A summary timeline of the key events in the Namenda Litigation is attached hereto as Exhibit L.

IX. LEGAL UNDERSTANDING AND STANDARD

73. As mentioned above, I am an attorney with over forty years of experience. I have particular knowledge of patent law, and I have spent my entire practice working in that area of the law. I am aware of certain legal doctrines, summarized in Exhibit M, which are relevant to the statements and opinions contained in this Report.

X. STATISTICAL LIKELIHOOD OF SUCCESS IN A HATCH-WAXMAN CASE - IN GENERAL

A. Background

74. Based on my experience, patent infringement cases are handled by attorneys who generally have developed expertise in the field of intellectual property litigation. These attorneys are found within a corporate setting as "in-house patent counsel" or at a law firm as "outside patent counsel." It is common for senior level corporate management to ask for its patent attorneys' views on the likelihood of success in a patent litigation, the likely length of time for the litigation, and the likely cost of the litigation. These requests are posed by both plaintiffs' and defendants' management in a patent litigation.

75. From my experience, it also is routine for management to rely upon its patent attorneys' responses. In my experience, corporate management often uses this type of information for various purposes including deciding whether to institute a suit, deciding whether to continue a suit, deciding whether to settle a suit and on what terms, establishing budgets, and for other planning purposes.

76. A person generally unfamiliar with patent infringement cases might be tempted to believe that, on average in patent infringement cases, the patent holder has a high probability of prevailing in the patent infringement case.

77. This person might make that assumption based on the understanding that:

- a U.S. patent examiner may have technical knowledge and years of experience from working at the USPTO.
- the examiner presumably thoroughly reviewed the patent application for compliance with U.S. patent law and procedures.
- the examiner found the patent application worthy of issuance into a U.S. patent.
- the Director of the USPTO signed the patent cover sheet and an official blue ribbon was appended to the original patent.

78. This person then may recall from high school civics class that an inventor has a constitutional right to exclude others from his or her discoveries[39].

79. Additionally, that person might also know that to "win" a patent litigation, the patent holder must establish that the accused infringer's product or its actions fall within *only one* of potentially many presumably valid patent claims[40].

80. Based solely on the above assumptions, a person generally unfamiliar with patent infringement litigation might think that, in the average patent infringement case, the patent holder has a greater than 50-50 chance of prevailing. However, experienced litigants and patent attorneys know better. In reality, there are other factors that need to be taken into account which significantly diminish the chance of the patent holder prevailing in a patent infringement litigation.

81. First, the patent holder has the burden of proof, by a "preponderance of the evidence," to establish infringement[41]. To prevail, the patent holder must demonstrate that the accused infringer's product or actions included each and every limitation found in a given claim.

---

[39] Article I, Section 8, Clause 8 of the United States Constitution empowers the United States Congress: "To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."

[40] A patent holder's property or exclusionary rights are defined by the "claims" that are found at the end of the U.S. patent. *See* Exhibit C. The number of claims in a patent varies from patent to patent. *See id.* From my experience, most patents contain many claims, particularly pharmaceutical patents.

82. From my experiences, the "preponderance of the evidence" standard in infringement determinations means that on an imaginary balance or scale, the weight of the evidence "tips" the scale slightly toward the patent holder (*i.e.*, >50% in the patent holder's favor such as 51% to 49%). *See also* Exhibit M. Should the evidence of infringement of a patent claim be absolutely equal (*i.e.*, 50-50), the accused infringer – not the patent holder – "wins" as to that patent claim. Looking at the other side of the same coin, should the patent holder fail to prove by a "preponderance of the evidence" that a given patent claim is infringed (*i.e.*, 50% or less in the patent holder's favor), the patent holder "loses" as to that patent claim. The accused infringer has no burden of proof in that regard.

83. Second, each patent claim does not necessarily present the patent holder with a "new" or "additional" opportunity to establish infringement. Different claims in the same patent often reference (*i.e.*, depend from) other claims in the patent. *See* Exhibit C. These "dependent claims" may reference (directly or indirectly) an independent claim and may also reference other dependent claims. Because of the dependent relationship, the dependent claims include all of the same claim limitations as found in the other claims from which they depend. In contrast, an independent claim does not depend from another claim. Therefore, the question of an accused infringer infringing these dependent claims often rises or falls together with respect to those claim limitations that are found in the claims from which they depend.[42]

84. Third, even if the patent holder proves infringement as to one or more claims, the accused infringer may nevertheless prevail by establishing various defenses by "clear and convincing evidence." For example, available defenses include claim invalidity and patent unenforceability. To prevail under the "clear and convincing" standard[43], the accused infringer must demonstrate that on an imaginary balance, the weight of the evidence "tips" the scales significantly toward the accused infringer.

85. Fourth, seasoned patent attorneys also know that a large number of different invalidity defenses are available to the accused infringer. For example, from 2008–2010 (*i.e.*, at the time of the Namenda Litigation), various validity challenges theoretically could have been made under 35 U.S.C. § 102 (*i.e.*, anticipation by a patent, printed publication, on sale bar, or public use, or inherency); under 35 U.S.C. § 103(a) (*i.e.*, obviousness); and

---

[41] Under the "preponderance of the evidence" standard, the patent holder must show that it is more likely than not that an assertion is true. *See* Exhibit M.

[42] If an "independent" claim is not infringed, then neither is any claim that depends, directly or indirectly, from it (because a "dependent claim" includes all of the limitations of the claim(s) from which it depends, directly or indirectly). *See* Exhibit M.

[43] The clear and convincing standard has been described as evidence which produces in the mind of the trier of fact an abiding conviction that the truth of the factual contentions is *highly probable*. *See* Exhibit M.

under 35 U.S.C. § 112 ¶ 1 (*i.e.*, enablement, best mode, or written description). Likewise, various enforceability challenges theoretically could have been raised including inequitable conduct during prosecution of the patent application or during prosecution of the patent term extension application.

86. Because a patent holder must prove infringement of at least one claim that also must survive all the accused infringer's validity and unenforceability challenges, experienced patent attorneys know that patent cases are not on average decided in the patent holder's favor. Thus, in my opinion, the chance of success for the patent holder to prevail in a patent litigation is not as likely as a person generally unfamiliar with patent infringement litigation might think.

B. Patent Litigation Statistics – Available Circa 2009–2010

87. Statistical studies have been undertaken to determine the likelihood of various events occurring in patent litigation, including overall likelihood of success. I am aware of three statistical studies that were publicly available around the 2009–2010 era[44]:

- Paul M. Janicke & LiLan Ren, *Who Wins Patent Infringement Cases?* 34:1 AIPLA Quarterly Journal[45], 1–43 (2006) ("**Janicke Paper**");
- Federal Trade Commission ("**FTC**"), *Generic Drug Entry Prior to Patent Expiration: An FTC Study* (July 2002) ("**FTC Study**"); and
- Adam Greene & D. Dewey *Steadman, Pharmaceuticals: Analyzing Litigation Success Rates*, RBC Capital Markets Industry Comment (January 2010) ("**RBC Study**").

88. The threshold question posited by the Janicke Paper was: "As between patent holders and accused infringers, who wins[46] in dispositive litigation that has proceeded through the Court of Appeals for the Federal Circuit?" Janicke Paper at 8. Janicke provides the following table summarizing the results:

[44] That is, at the time when Forest, Merz, and the Generic Companies settled the Namenda Litigation.

[45] The AIPLA Quarterly Journal is published by the American Intellectual Property Law Association, a national intellectual property law bar association with nearly 14,000 members, most of whom are lawyers in private and corporate practice, in government service, and in the academic community.

[46] Janicke defines "winning" as "a judgment in favor of a particular party at the Federal Circuit Court of Appeals." Janicke Paper at 4. Thus, a "win" would mean "a case in which, as it leaves the Federal Circuit, at least one claim of one patent is finally adjudicated to have been infringed and not invalid or unenforceable (*i.e.*, a win for the patent owner), or in which it has been finally determined that no claim has these characteristics (a win for the accused infringer)." *Id.* (footnote omitted).

Table 1. Win Rates

YEAR	DISPOSITIVE CASES	# WON BY PATENT OWNER	% WON BY PATENT OWNER
2002	71	20	28.2%
2003	101	25	24.8%
2004	90	19	21.1%
ALL 3 YEARS	262	64	24.4%

Id.

89. Consistent with the "Win Rates" Table above, Janicke noted that accused infringers win patent infringement lawsuits "at a rate of three to one." *Id.* at 3. In other words, accused infringers win 75% of the time while patent holders win 25% of the time.

90. Janicke summarized the findings for the 262 cases from various industries that were studied as follows:

> about 25% of the 262 dispositive cases were won by the patent owner (according to [Janicke's] definition of winning) and the other 75% by the accused infringer. This was not surprising in light of previous writers' conclusions that about 45% of litigated patents are held invalid, and additional statistics showing that the great majority of determinations on the infringement issue are against the patent owner and in favor of the accused infringer.

Id. at 5–6 (footnotes omitted).

91. Janicke explained the reasons for a lower percentage of winning for the patent holders as follows, "[s]ince the patent owner must prevail on both the infringement and validity/enforceability fronts to win the case, it should not be too surprising that patentee victories are relatively infrequent." *Id.* at page 8.

92. Thus, the Janicke Paper confirms my above opinion that the chance of success for the patent holder to prevail in a patent litigation is not as high as a person generally unfamiliar with patent infringement litigation might think. As Janicke explained, on average, accused infringers prevail in patent litigations statistically much more often than patent holders prevail. *Id.*

93. The FTC Study is of particular interest for my Report because it focuses on pharmaceutical patents rather than patents in all industries. For the study, the FTC "subpoenaed documents and information from brand-name and generic drug manufacturers, and examined instances since 1992 in which generic applicants filed an application with FDA seeking to enter the market with a generic version of a drug product prior to expiration of the brand-name drug products' patents." FTC Study at ii (footnote omitted).

94. The FTC Study showed that "[g]eneric applicants have prevailed in 73 percent of the cases in which a court has resolved the patent dispute." *Id.* at vi. The FTC Report provides the following table summarizing the results:

Table 2-4 Patent Litigation Results per Drug Product

Result of Litigation	Number of NDAs
Generic Applicant Wins	29
Brand-Name Company Wins	11
Total	**40**

Id. at 20.

95. Specifically, the FTC Study found that:

> [g]eneric applicants prevailed for 29 out of 40 drug products (or 73 percent). Decisions involving 14 drug products held that the generic applicant did not infringe the patent, decisions involving 11 drug products held that the relevant patent(s) invalid, and in 4 cases, the brand-name company abandoned the litigation with the first generic applicant before a decision of a court.

Id.

96. Thus, the FTC Study also confirms my above opinion that the chance of success for the patent holder to prevail in a patent litigation is not as high as a person generally unfamiliar with patent infringement litigation might think. As explained in the FTC Study, on average, generic companies prevail in ANDA patent litigations statistically much more often than brand-name companies prevail.

97. The results of the RBC Study are not inconsistent with the conclusions of the Janicke Paper or the FTC Study. The RBC Study analyzed "over 370 court rulings since the beginning of the decade [2000–2009] to establish litigation success rates by company, court and judge." RBC Study at 3. The RBC Study concluded that over the 2000–2009 decade, "the overall success rate for the generic drug industry is 48% for cases that have gone to trial." *Id.* at 1; *see also id.* at 4. The RBC study, however, explained that "when you take into account [both] settlements and cases that were dropped, the **success rate for generics jumps to 76%.**" *Id.* at 4 (emphasis in original). The RBC Study also recognized that "[t]he number of settlements in 2009 reached an all-time high." *Id.* at 8.

98. The RBC Study authors hypothesized that based on the incentives of the Hatch-Waxman Act, every patented product would be challenged. *Id.* at 4. As long as settlements and dropped cases are considered a "success" for generics, the RBC study findings support the authors' hypothesis that every patent would be challenged by a generic. With a 76% success rate, the potential payoff of a first-to-file Paragraph IV challenge is generally worth the cost of litigation. The RBC Study also found that the following generic defendants – Teva (78%), Lupin (75%), Sun (67%), Mylan (64%), Ranbaxy, (63%), Dr. Reddys (61%), and Apotex (43%) – who were involved in the Namenda Litigation and listed below, were particularly successful[47] in other patent litigations in which they were involved. *Id.* at 5 Ex. 4.

Exhibit 4: Best Generic Challengers 2000-2009, Greene and Steadman, *Pharmaceuticals: Analyzing Litigation Success Rates*" (January 15, 2010)

Best Overall Success Rate		Cases Won As % of Decisions		Cases Lost As % of Decisions		Cases Settled/Dropped As % of Total P4s		Most Number Of Concluded P4 Cases	
Perrigo	100%	Perrigo	100%	Apotex	86%	Perrigo	88%	Teva	108
Watson	90%	Sandoz	79%	Ranbaxy	78%	Watson	74%	Watson	39
Sandoz	88%	Par	67%	Dr. Reddy's	78%	KV Pharm	71%	Mylan	25
Par	87%	Impax	67%	Sun	75%	Lupin	63%	Sandoz	24
KV Pharm	86%	Actavis	67%	Lupin	67%	Par	60%	Apotex	21
Impax	86%	Watson	60%	URL Pharma	67%	Impax	57%	Ranbaxy	19
Actavis	83%	Teva	53%	Mylan	56%	Sun	56%	Dr. Reddy's	18
Teva	78%	KV Pharm	50%	KV Pharm	50%	Teva	53%	Par	15
Lupin	75%	Mylan	44%	Teva	47%	Ranbaxy	53%	Impax	14
Sun	67%	Lupin	33%	Watson	40%	Dr. Reddy's	50%	Sun	9
Mylan	64%	URL Pharma	33%	Par	33%	Actavis	50%	Perrigo	8
Ranbaxy	63%	Sun	25%	Impax	33%	Sandoz	42%	Lupin	8
Dr. Reddy's	61%	Ranbaxy	22%	Actavis	33%	URL Pharma	40%	KV Pharm	7
URL Pharma	60%	Dr. Reddy's	22%	Sandoz	21%	Mylan	36%	Actavis	6
Apotex	43%	Apotex	14%	Perrigo	0%	Apotex	33%	URL Pharma	5

**Includes predecessor firms.*

99. Based on the above statistics involving pharmaceutical patents, in my opinion, it is reasonable to conclude that, on average, a generic defendant in a Hatch-Waxman patent infringement case had approximately a 65–75% chance of success. *See id.* This opinion

[47] Including dropped and settled litigations.

also is consistent with the above statistics as found in the Janicke Paper and in the RBC Study, as explained above. Viewed conservatively, the statistics make clear that, on average, a generic defendant in a Hatch-Waxman patent infringement case has a greater than a 60% chance of success.

100. As a result, in my opinion, Forest, Merz, and the Generic Companies should have known around the time of the settlements that, on average, generic companies prevail in ANDA patent litigations statistically much more often than brand-name companies prevail.

101. Taking all of the above into consideration, in my opinion, a reasonable and competent patent attorney would have realized that, *based on statistics*, on average, in a patent litigation the litigants' overall chance of success was about 65–75% in favor of the generic company and 35–25% in favor of the brand company.

C. Patent Litigation Statistics – Available After 2009–2010 Era

102. In preparing this Report, I did not rely on any post-2009–2010 patent litigation statistics because that information was not available at the time the Namenda Litigation settled. Any post 2009–2010 statistical information could not have been considered by Forest, Merz, or the Generic Companies and their patent counsel in assessing the likelihood of success in the Namenda Litigation prior to settlement. For completeness, however, post-2009–2010 studies are listed and discussed below:

- C. Scott Hemphill & Mark A. Lemley, *Earning Exclusivity: Generic Drug Incentives and the Hatch-Waxman Act*, 77:3 Antitrust Journal, 947–89 (2011) ("**Hemphill Paper**");
- Mark A. Lemley, *Where to File Your Patent Case*, 38:4 AIPLA Quarterly Journal Pages 1–37 (Fall 2010) ("**Lemley Study**"); and
- PricewaterhouseCoopers, *Patent Litigation Study: Big cases make headlines, while patent cases proliferate* (2013) ("**PwC Study**").

103. In my opinion, these three studies generally can be reconciled with the observations in the Janicke Paper, the FTC Study, and the RBC Study.

104. The Hemphill Paper supports the RBC Study position that increased settlements between brand-name and generic companies can explain the difference in success rate for the generic company as reported in the FTC Study (73%) in 2002 and the RBC Study (48%) in 2010. *See* Hemphill Paper at 979. According to the Hemphill Paper, a decline in the generic success rate between the time of the FTC Study and the RBC Study was likely traceable to "an increase in settlements in weak-patent cases." *Id.* at 979.

105. Table 3 of the Lemley Paper summarizes "Patentee Win Rate in Districts with 25 or More Outcomes" from 2000–2010. Lemley Paper at 8–10. According to the Lemley Paper, the "claimant win percentage" in the District of Delaware – the main forum in which the Namenda Litigation was litigated – was 45.3%. *Id.* at 8. Consistent with the Janicke Study, the Lemley Paper also showed that, nationwide, patent holders prevailed in the district courts much less than half the time (*i.e.*, 32.5%). *Id.* at 10. In other words, accused infringers prevailed much more (*i.e.*, 67.5%) on a national basis, in district court. The Lemley Paper, thus, generally supports the earlier findings of the FTC Study regarding generic success rates from 2000–2009.

106. The PwC Study considered the period from 1995–2012. The PwC Study reported that patent holders' "overall success rate (trial and summary judgment combined) for all industries . . . was approximately 32%" during the study period. PwC Study at 17. In other words, overall, accused infringers won 68% of the cases included in the PwC Study. *Id.*

107. More applicable to the present Namenda Litigation, PwC noted that the patent holders' success rates for "biotechnology/pharma" patents in the 1995–2012 period was about 38%. *Id.* at Chart 6e, 17. In other words, generic companies prevailed 62% of the time. *Id.* PwC also noted that from 2006 through 2012, "ANDA litigation success rates [for the brand-name company] have ranged from a low of 22% to a high of 83%."[48] *Id.* at 28. The authors postulated that "the sample size . . . was low, possibly explaining the wide swings in success rates." *Id.* A reason for a low sample size was "[b]ecause the majority of ANDA Litigations continue to end in settlement . . . ." *Id.*

108. In my opinion, these post-2009–2010 era reports and studies, in general, demonstrate that generic companies prevailed much more often than brand-name companies in patent litigations during the applicable study period, and are consistent with the three studies that were available around 2009–2010.

109. However, although helpful to provide some perspective, statistics present broad-based historic averages and do not necessarily present the whole picture. Each case has its own set of issues and facts that need to be considered on an individual basis (*e.g.*, actual defenses being alleged, claim language and scope, and ability to "engineer around" claim language). Thus, the merits of the Namenda Litigation also must be evaluated when considering the chance of success as will be considered in Section XI of this Report.

[48] With respect to ANDA litigations, for completeness I note that the PwC Study only analyzed post-2006 decisions (*i.e.*, decisions from 2006-2012) and thus carved out ANDA litigation decisions prior to 2006, including the years covered by the FTC Study. *See* PwC Study Chart 11c, 28.

XI. EVALUATION OF THE MERITS OF THE '703 PATENT CLAIMS

A. Approach to Evaluation

110. In my experience, patent lawyers are often called upon to advise senior corporate management or clients as to their chances of success in a patent litigation. They are often called upon to provide such advice when a patent owner is deciding whether to file an infringement suit on a patent that it owns, when an accused infringer is considering whether to engage in patent litigation or cease and desist from contemplating or making allegedly infringing sales, and during settlement discussions. As a former Chief Patent Counsel, I personally provided such assessments regarding patent litigations to senior management.

111. In my opinion, a reasonable and competent patent attorney faced with a request to evaluate the likelihood of success in a patent litigation would recognize the overall difficulty for a patent owner to prevail. The attorney would be aware of the statistical studies that I described above, *see* Section X, and would have his or her own experience in patent litigations that in all likelihood would confirm the challenges for a patent owner prevailing in a patent infringement case[49].

112. In addition, the attorney would of course evaluate the particular merits of the case-at-hand to see if there were reasons to believe that the patent-at-issue was particularly "strong" (*i.e.*, no viable patent defenses) or particularly "weak" (*i.e.*, one or more significantly viable patent defenses). In other words, the attorney may look for "red flags" that may be of concern (*e.g.*, assignments, declarations, anomalies during prosecution, substantial noninfringement arguments, substantial invalidity arguments, uncited prior art, correspondence, and corresponding foreign patent applications[50] and their prosecution).

---

[49] In saying this, I recognize that the cases reflected in the statistical studies are ones that did not settle prior to a final judgment, whereas the Namenda Litigation did. Thus, one could argue that the cases reflected in the statistical studies might not be representative of cases that do settle. But for several reasons, in my opinion, a reasonable and competent patent attorney would nevertheless ascribe some predictive value to those studies. First, even if he or she believed that the likelihood of success in the population of cases that do not settle differed from the likelihood of success in the population of cases that do settle, from my experience patent infringement attorneys tend to rely on the best available information. And, from what I could find, there is no data on likelihood of success that is specific to the population of cases that settle. Thus, the best available statistical data is that reflected in the statistical studies. Second, he or she would know that, if the case does not settle, it will become part of the population of cases that are reflected in the statistical studies. Thus, the statistical studies offer some guidance on statistical likelihood of success if the case does not settle. Third, I have seen no evidence suggesting that the likelihood of success in the population of cases that do not settle does in fact differ, or how it might differ, from the likelihood of success in the population of cases that do settle. If anything, the Hemphill Paper suggests that in Hatch-Waxman cases a settlement may reflect that the patent is at the "weak" end of the spectrum.

[50] Forest and Merz argued that the foreign proceedings "do not help Mylan meet its burden of overcoming the statutory presumption of validity of the '703 patent" and that "the Federal Circuit has admonished attempts to

113. For example, the calculus that the attorney would use to determine the merits of the case-at-hand also requires that the attorney evaluate the *type* of patent being evaluated and, in particular, the *type* of claims in the patent. Based on my experience in the pharmaceutical patent field, and in the broadest sense, there are three types of pharmaceutical patents:

1. First Tier patents, such as those that claim new pharmaceutically active compounds (*i.e.*, contain claims directed to the compound *per se*);

2. Second Tier patents, such as those that claim a new pharmaceutical use of a known compound where the use was not previously contemplated (*i.e.*, method of treatment claims covering a different and unique pharmaceutical indication than previously indicated for the compound); and

3. Third Tier patents, such as those that claim a new pharmaceutical use of a known compound but where the use generally falls into the same or similar category as previously indicated for the compound (*i.e.*, method of treatment claims covering a pharmaceutical indication similar to that previously indicated for the compound).

114. By way of illustration of a First Tier patent and a Second Tier Patent consider Pfizer's drug Viagra®. In its First Tier patent[51], the active ingredient of Viagra (*i.e.*, sildenafil citrate) was covered by compound and method of treatment claims for cardio-protective affects. As experience with the drug was gained through clinical (*i.e.*, human) studies, the active ingredient also became the subject of a Second Tier patent[52] for the indication which today it is commonly known. In its First Tier patent, the active ingredient was indicated for angina, hypertension, heart failure, and atherosclerosis. In its Second Tier patent, it was indicated for male erectile dysfunction – again the latter being very unique and different than the previously claimed indications in its First Tier patent.

115. By way of illustration, *if* Pfizer had also filed another patent application directed to an additional cardio-protective affect (*e.g.*, treating arrhythmias), this additional patent would be considered, what is described above as a Third Tier patent because the First Tier patent was also directed to various cardio-protective affects.

---

invalidate U.S. patents with foreign rulings on patentability of foreign patents under foreign patent law." Pretrial Order, Exhibit 11, ¶ 295 (citing *Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc.*, 21 F.3d 1068, 1072 n.2 (Fed. Cir. 1994)). Even in view of *Heidelberger* however, in my opinion a reasonable and competent patent attorney would have reviewed the foreign patents and their associated prosecution for "red flags."

[51] U.S. Patent No. 5,250,534.

[52] U.S. Patent No. 6,469,012.

116. Although there are exceptions, based on my experience, pharmaceutical patent attorneys would prefer asserting First Tier patents before asserting Second and Third Tier Patents. For example, it generally is more difficult to mount an invalidity attack[53] against a First Tier patent because it usually includes patent pharmaceutical data (*i.e.*, characterization and activity data) on the claimed compounds and usually contains a specific claim (*i.e.*, species claim) directed to the compound that is being contemplated for marketing as a pharmaceutical, thus making it more difficult to be attacked. Moreover, at least in the Hatch-Waxman context, it is difficult to mount a noninfringement defense as to a First Tier Patent because generic products are required by law to use the same active ingredient as is found in the brand product.

117. Should there be no First Tier patent to assert (*e.g.*, known compound or the First Tier patent expired), based on my experience, pharmaceutical patent attorneys then would prefer asserting a Second Tier patent to a Third Tier patent.

118. On the one hand, the presence within the Second Tier patent specification of data directed to a unique, not previously contemplated indication would make it more difficult to mount an invalidity attack based on obviousness. It also generally can be more difficult to mount an invalidity attack against a Second Tier patent *when* the patent includes clinical pharmaceutical data directed to the treatment being claimed[54].

119. On the other hand, for example, Second Tier patents run the risk of being invalidated if the new indication was achieved, even if unappreciated at the time, when the compound was given for the previous intended use. For example, if aspirin[55] were given to a patient suffering from pain (*i.e.*, the previous use), but a cardio-protective affect (*i.e.*, the new intended use) was also obtained, the validity of a patent claim directed to the new cardio-protective method of treatment would likely be in question. Taken collectively, in my opinion, a reasonable pharmaceutical patent attorney would be cautious in asserting a Second Tier patent but would consider asserting the Second Tier patent if no First Tier patent were available.

120. Should there be no First or Second Tier patents to assert, based on my experience, a pharmaceutical patent attorney then would consider asserting a Third Tier patent like the '703 patent. Because a Third Tier patent is directed to the treatment of a new indication that falls within the same or similar category as a previously disclosed indication for the

[53] Assuming, of course, no disclosure in the prior art that anticipates or renders obvious the claimed compounds and the patent specification satisfies the other requirements for patentability.

[54] Method of treatment claims require that data be present in the specification confirming that the compounds can be used for their intended purpose. Because the intended purpose is the treatment of a specific disease, should data be lacking or deficient in claim scope, then the patent would be open to invalidity attacks.

[55] U.S. Patent No. 644,077.

compound, such patent would be prone to invalidity attacks. Moreover, sufficient data, preferably clinical data, would be required to be presented in the patent specification to support the new indication. And, like Second Tier patents, Third Tier patents also run the risk of being invalidated if the new treatment was achieved when the compound was given for the previous intended use. Moreover, it may be possible to mount a substantial noninfringement defense as to Second and Third Tier patents if the accused infringer's method of use can be distinguished from the patented method of use. Taken collectively, in my opinion, a reasonable and competent pharmaceutical patent attorney would be cautious in asserting a Third Tier patent.

121. In making the above assessment, the patent attorney would investigate the facts, but would not necessarily be a person of ordinary skill with respect to the technology involved in the patent. Instead, the patent lawyer would attempt to become informed about the disputed factual and legal positions presented by the parties and then consider the likely outcomes on those disputed issues when advising management or the client.

122. In this Report, I have interpreted my assignment (*i.e.*, that I evaluate what a reasonable and competent patent attorney would have advised litigants in the Namenda Litigation at the time they settled in terms of their likelihood of success) to mean that I should conduct the above-described assessment.

123. I would expect that all of the parties to the Namenda Litigation received this kind of advice from their attorneys before deciding to settle. However, I understand that the particular advice that the parties received would be subject to an assertion of the attorney-client privilege.

124. Additionally, while Mylan and the other Generic Companies raised numerous invalidity defenses. I have concentrated on what I believe are some of the more compelling defenses[56]. In my opinion, a reasonable and competent patent attorney at the time of settlement also would concentrated on what he or she believed were some of the more compelling defenses.

B. Invalidity Defenses

1. 35 U.S.C. § 102 – Anticipation

125. Under 35 U.S.C. § 102, a claim is invalid for anticipation if "a single prior art reference discloses each and every limitation of the claimed invention." *Schering Corp. v. Geneva*

[56] My concentrating on only a few of these many defenses should not be construed as an acknowledgement in any way of the strength or weaknesses of the remaining defenses. I have limited my evaluation to these few defenses for efficiency purposes recognizing that an accused infringer has merely to prevail on only one defense that is applicable to all the asserted claims.

Pharm., 339 F.3d 1373, 1377 (Fed. Cir. 2003); *see also Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002). Thus, each and every element of a claim, as properly construed, must be found either explicitly or inherently in a single prior art reference. *See Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008).

126. A patent claim however, "'cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled.'" *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research,* 346 F.3d 1051, 1054 (Fed. Cir. 2003) (quoting *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003)). Furthermore, a prior art reference need not demonstrate utility in order to serve as an anticipating reference under §102. In *In re Hafner*, the court stated that "a disclosure lacking a teaching of how to use a fully disclosed compound for a specific, substantial utility or of how to use for such purpose a compound produced by a fully disclosed process is . . . entirely adequate to anticipate a claim to either the product or the process and, at the same time, entirely inadequate to support the allowance of such a claim [under 35 U.S.C. § 112]." 410 F.2d 1403, 1405 (C.C.P.A. 1969)[57].

127. In the Namenda Litigation, Mylan bore the burden of establishing that the '703 patent claims were anticipated under 35 U.S.C. § 102 by clear and convincing evidence. *Orion IP, LLC v. Hyundai Motor Am.*, 605 F.3d 967, 675 (Fed. Cir. 2010).

a. Mylan's Position

128. Mylan's position in the Namenda Litigation was that the claims of the '703 patent were invalid as anticipated by prior art disclosing the oral administration of memantine to patients diagnosed with dementia disorders, including patients with Alzheimer's disease who would have been clinically diagnosed with Alzheimer's disease. *See, e.g.*, Pretrial Order, Exhibit 12, ¶¶ 119–59.

b. Forest and Merz's Position

129. Forest and Merz's position in the Namenda Litigation was that none of the references relied upon by Mylan (regarding either memantine or amantadine) anticipated any asserted claim of the '703 patent. Forest and Merz argued that none of the alleged prior art references relied upon by Mylan disclosed the oral administration of memantine (or

[57] *See also In re Schoenwald*, 964 F.2d 1122, 1124 (Fed. Cir. 1992); *see also In re Samour*, 571 F.2d 559, 563–64 (C.C.P.A. 1978); *see also In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349–52 (Fed.Cir.2002) (finding anticipation where applicant sought a patent based on a new use for a previously disclosed method); *see also In re Donohue,* 632 F.2d 123, 126 n. 6 (C.C.P.A. 1980) (*citing In re Samour,* 571 F.2d at 563–64) (noting that "proof of utility is not a prerequisite to availability of a prior art reference under 35 U.S.C. § 102(b)"); *see also Application of Lukach*, 442 F.2d 967, 969 (C.C.P.A. 1971) (recognizing that there are "anomalies between the requirements for claim-anticipating disclosures and for claim-supporting disclosures").

any other claimed adamantane derivative) to a live person diagnosed with dementia of the Alzheimer's type, as characterized by accepted diagnostic criteria. Pretrial Order, Exhibit 11, ¶¶ 115-126; 370-371.

c. Analysis[58]

130. Mylan contended that claims 1-3, 6, 8, 10-12 and 14-19 of the '703 patent were anticipated by each of the following references (collectively, the "**Memantine Studies**"):

- Tempel (1989) "Memantine in organic brain syndrome – Can disturbed social and self-care behaviors be improved?" *Therapiewoche* 39:946-952;
- Ambrozi & Danielczyk (1988) "Treatment of impaired cerebral function in psychogeriatric patients with memantine – results of a phase II double-blind study" *Pharmacopsychiatry* 21:144-146;
- Marcea & Tempel (1988) "Effect of memantine versus dh-Ergotoxin on cerebro-organic psychosyndrome" *Therapiewoche* 38:3097-3100; and
- Schäfer & Thiery (1984) "Memantine improves the cerebral performance in the elderly" *Psycho.* 12:8-18.

Pretrial Order, Exhibit 12, ¶ 133.

131. Mylan contended that each of those publications showed that prior to the filing of the '703 patent, "studies were published on the effective treatment of OBS [Organic Brian Syndrome] patients with memantine." *Id.* Mylan contended that those references anticipate the claims of the '703 patent because "the subpopulation of Alzheimer's disease patients claimed by the '703 patent is immediately envisioned by the genus disclosed in th[o]se references." *Id.* at ¶ 159.

132. In support of this assertion, Mylan relied on the expert opinion testimony of Dr. Paul Fishman, M.D., Ph.D. *See* Fishman Report at ¶ 56. In rebuttal, Forest and Merz relied on the expert opinion testimony of Dr. Martin R. Farlow, M.D., who concluded that those references do not anticipate the claims of the '703 patent because the references do not disclose "administration of memantine to a 'patient diagnosed with Alzheimer's disease,' *i.e.*, a patient specifically diagnosed with DAT[59] in accordance with the criteria of DSM-III-R, NINCDS-ADRDA, or other criteria that were generally accepted at that time." Farlow Report at ¶ 70.

[58] For a more detailed discussion of the applicable law, see Exhibit M.

[59] DAT refers to "dementia of the Alzheimer's type." Farlow Report at ¶ 31.

133. Both experts fundamentally agreed that OBS[60] is a general term that encompasses a number of psychiatric diseases associated with "decreased mental function." Fishman Report at ¶ 11; Farlow Report at ¶ 74. Dr. Fishman explained that one form of OBS is dementia. Fishman Report at ¶¶ 11–12.

134. Dr. Fishman further noted that "the vast majority of patients with dementia suffer from Alzheimer's disease." Fishman Report at ¶ 22. In his deposition, Dr. Fishman confirmed that in patients he examined that had been diagnosed with OBS, for "the largest single group of patients, the specific diagnosis was that of Alzheimer's disease." Fishman Dep. Transcript, *Forest Labs. Inc. v. Cobalt Labs. Inc.* (Jan. 20, 2010) ("**Fishman Dep.**") at 141:16–142:17[61].

135. In support of the statement in his Report, Dr. Fishman noted that the Diagnostic and Statistical Manual of Mental Disorders (Third Edition — Revised, 1987) ("**DSM-III-R**") stated that:

> '[c]ertain degenerative Dementias have traditionally been referred to as Senile and Presenile Dementias, the distinction being arbitrarily based on age at onset over 65. ***Nearly all of these cases are associated with the histopathologic changes of Alzheimer's disease.*** Although the definitive diagnosis of Alzheimer's disease is dependent on histopathologic data, there is a growing consensus that there is a high correlation between this pathology and a particular clinical picture.'

Fishman Report at ¶ 22 (quoting DSM-III-R, at 19).

136. Thus, Dr. Fishman noted that "with regards to senile and presenile dementia, the DSM-III-R recognized in 1989 that nearly all organic mental disorder patients suffering from dementias arising in the senium and presenium suffer from Alzheimer[']s disease." *Id.*

137. In his report, Dr. Farlow did not dispute this testimony, but noted that OBS "would have no bearing on whether a patient was diagnosed with DAT in accordance with accepted criteria." Farlow Report at ¶ 72. During his deposition, Dr. Farlow also noted that OBS "tends to be a vague concept that has been defined in different ways by different . . . people in literature." Farlow Dep. Transcript, *Forest Labs. Inc. v. Cobalt Labs. Inc.* (Jan.

[60] According to Dr. Fishman, "OBS was one of several terms used in the 1980's to describe patients with decreased mental function, including organic mental disorder . . . cerebro-organic psycho-syndrome . . . [and] 'organic dementia', where 'dementia' is defined as 'the loss or impairment of higher mental functions.'" Fishman Report at ¶ 12 (citations and footnote omitted).

[61] Dr. Fishman went on to say that some of the OBS patients that he was not able to render a more specific diagnosis than OBS, also possibly suffered from Alzheimer's disease. Fishman Dep. at 143:6-13.

18, 2010) ("**Farlow Dep.**") at 84:15-85:5. Dr Farlow acknowledged, however, that he was not aware of any definition of OBS that would "exclude" or "not include patients with Alzheimer's disease." *Id.* at 85:6-86:10. Furthermore, Dr. Farlow admitted that in 1985, he considered OBS to include patients diagnosed with Alzheimer's disease. *Id.* at 92:22-93:3.

138. With respect to the Schäfer and Thiery 1984 publication, Dr. Fishman observed that in that study memantine was administered to patients diagnosed with "organic brain syndrome, cerebrovascular insufficiency, and protracted functional psychoses with signs of depression." Fishman Report at ¶ 27 (internal quotation marks omitted). Dr. Fishman observed further that the patients "were evaluated on the basis of electroencephalography tests, clinical chemistry tests, as well as several psychometric testing scales . . . ." *Id.* at ¶ 29. Dr. Fishman concluded "that one of ordinary skill in the art in 1989 would have understood that the Schäfer & Thiery study was evaluating characteristics commonly seen in patients suffering from dementia, including Alzheimer's disease, in an attempt to investigate whether memantine improved those characteristics." *Id.* at ¶ 30. Based on my review of his report, Dr. Farlow did not dispute this conclusion.

139. With respect to the Marcea & Tempel 1988 publication, Dr. Fishman observed that in that study the patients were recruited based on the "clinically recognized ICD.9 criteria (290.0, 290.1 and 290.4)." *Id.* at ¶ 33. Dr. Fishman noted that this "criteria includes senile dementia, presenile dementia and arteriosclerotic dementia, including patients diagnosed with Alzheimer's disease." *Id.* Dr. Farlow agreed with this conclusion, but noted that "the reference to ICD-9 criteria in *Marcea* does not indicate that any specific patient was diagnosed with DAT in accordance with accepted diagnostic criteria." Farlow Report at ¶ 94.

140. Dr. Fishman further observed that:

> [p]atients were evaluated using several psychometric tests, including: (a) Functional psychosis scale; (b) Plutchik scale for geriatric findings and (c) SCAG (Sandoz Clinical Assessment Group) test. The SCAG was used as a measure of cognition to demonstrate improvement by memantine in treatment of Alzheimer's disease in Plaintiffs' IND application to the US FDA.

Fishman Report at ¶ 34 (citing Gortelmeyer & Erbler, "Memantine in the Treatment of Mild to Moderate Dementia Syndrome: A Double-Blind Placebo-Controlled Study", Drug Res. (1992), 42:904-913).

141. Dr. Fishman stated that "[i]t is my opinion that one of ordinary skill in the art in 1989 would have understood that the Marcea & Tempel study employed the SCAG tests in an attempt to investigate improvements in patients suffering from dementia, including

Alzheimer's disease." *Id.* at ¶ 36. Dr. Fishman further stated that based on the selection and exclusion criteria that "it is very likely that the target population consisted primarily of demented patients." *Id.* at ¶ 38.

142. Dr. Farlow did not specifically disagree with this conclusion, but instead asserted that "a person of ordinary skill would not have been able to determine whether any of the patients in *Marcea* suffered from DAT." Farlow Report at ¶ 96 [62].

143. With respect to the Ambrozi & Danielczyk 1988 publication, Dr. Fishman stated that the publication "disclose[d] a 'double-blind phase II trial [investigating] whether Memantine has the ability to influence the mnestic disorders characteristic of dementia as one category of the organic mental disorders (DSM-III)." Fishman Report at ¶ 39.

144. With respect to the tests disclosed in Ambrozi & Danielczyk, Dr. Fishman stated that:

> Ambrozi & Danielczyk used a variety of tests that measured improvements in vigilance and other attributes affected in Alzheimer's disease patients, including: (a) the Flicker Frequency Analysis, which is a 'measurement vigilance, i.e. of the state of alertness'; (b) the Digit Span Test, which 'determines attention and short-term memory'; and (c) the Mosaic Test, which is a 'sensitive indicator of premature cerebral degeneration.' Ambrozi & Danielczyk, at 145. It is my opinion that one of ordinary skill in the art in 1989 would have understood that the Ambrozi study was measuring vigilance, attention, short-term memory and premature cerebral degeneration in an attempt to investigate improvements in patients suffering from dementia, including Alzheimer's disease.

Id. at ¶ 41. In his report, Dr. Farlow did not dispute this conclusion by Dr. Fishman[63].

---

[62] However, in his deposition, Dr. Farlow acknowledged that he did not form any opinions when preparing his report on whether the above Poutschik [sic] Geriatric Rating Scale was an appropriate test to be used in the diagnosis of patients with Alzheimer's disease. At the deposition, he expressed no opinion regarding the test. Farlow Dep. at 205:21-23.

Dr. Farlow admitted that he would have to review the above Functional Psychosis Scale B test to form an opinion as to whether it was an appropriate test to be used in the diagnosis of patients with Alzheimer's disease. At the deposition, he expressed no opinion regarding the test. *Id.* at 204:16-205:8.

Dr. Farlow also admitted that he did not form an opinion when preparing his report on whether the above SCAG test was an appropriate test to be used in the diagnosis of patients with Alzheimer's disease. *Id.* at 196:8-198:4. He acknowledged, however, that he had "personally been involved in trials where – or a trial where it was used." *Id.* at 196:13-20.

[63] Regarding the above Digit Span test, Dr. Farlow explained that "it was part of the Cerad battery . . . [that] was used by neuropsychologists in [the relevant] time period in the United States." Farlow Dep. at 203:7-13. And, that "[c]ertainly in conjunction with abnormalities or deficits in other tests, it was looked at and was useful in assessing

145. With respect to the Tempel 1989 publication, Dr. Fishman stated that this publication disclosed a study of patients diagnosed with "medium grade organic brain syndrome (OBS)" which "effectively excluded patients with severe depression, psychosis since treatment with anti-depressant or anti-psychotic medication was not allowed"; "effectively excluded" patients with delirium "because the length of illness prior to treatment ranged from one month to twelve (12) years"; and that "laboratory testing prior to administration of memantine would have also excluded patients suffering from metabolic abnormalities that depress mental function[]." *Id.* at ¶ 44.

146. With respect to the tests disclosed in Tempel 1989, Dr. Fishman stated that:

> Tempel used a variety of tests that measured improvements in vigilance and other attributes affected in Alzheimer's disease patients, including: (a) SCAG, which as described above, measures changes with treatment in cognitive disturbances, social behavior, lack of motivation, affective disturbances and somatic disturbances; (b) the Profile of Mood States (POMS) test, which measures a subject's mood and state of depression, fatigue, activity drive and moroseness; (c) physical symptoms; and (d) sleep disturbances. It is my opinion that one of ordinary skill in the art in 1989 would have understood that the Tempel study was employing the SCAG and POMS tests, as well as a measurement of sleep disturbances in an attempt to investigate improvements in patients suffering from dementia, including Alzheimer's disease.

Id. at ¶ 46[64].

147. Ultimately, Dr. Fishman concluded that "the Tempel study necessarily administered memantine to patients suffering from Alzheimer's disease and one of ordinary skill in the art would have reached that same conclusion upon reading the Tempel reference in 1989." *Id.* at ¶ 48. As support for his above conclusion, Dr. Fishman pointed to an internal Merz memo (the "**Merz Memo**") regarding the Tempel study, which concluded

---

patients and determining that they had overall a problem with cognitive deficits in more than one domain." *Id.* at 203:20-24.

Dr. Farlow also acknowledged that he did not specifically review the Mosaic Test in connection with forming his opinions in the Report. *Id.* at 207:5-8. And, that he would need to review it to form an opinion as to whether it was an appropriate test to be used in the diagnosis of patients with Alzheimer's disease. *Id.* at 204:9-15. Other than acknowledging that in the past he was familiar with the Mosaic Test, he did not express an opinion regarding the test at the deposition. *Id.*

[64] Regarding Dr Farlow's comments on the SCAG Test, see Report, Footnote 62.

At his deposition, Dr. Farlow also explained that he did not specifically review the POMS Test in connection with forming his opinions in his Report. Farlow Dep. at 206:15-207:4. Dr. Farlow did not express an opinion regarding the test at the deposition. *Id.*

that "**[a]ll patients participati[ng] in the study suffered from organic brain syndrome (OBS; OPS — ICD-No. 290.0) resulting from Alzheimer's disease or cerebral sclerosis**." *Id.* at ¶ 49 (emphasis in original) (quoting Merz Memo at MERZ0019050) [65, 66, 67].

148. Dr. Farlow disagreed with Dr. Fishman "that the exclusion criteria in *Tempel* necessarily would have resulted in a population consisting of patients suffering from DAT." Farlow Report at ¶ 112.

149. As to the Merz Memo, Dr. Farlow dismissed Dr. Fishman's opinions and then expressed reluctance for him or Dr. Fishman to opine on that document:

> I note that Dr. Fishman's opinion is supported in part by his review of internal Merz documents that purportedly characterize the study population in *Tempel*. I understand that the relevant questions regarding *Tempel* are whether the *Tempel* study ***as published*** would anticipate or render obvious any claim of the '703 patent, from the perspective of a person of ordinary skill in the art. Not having been an employee of Merz, I cannot opine on what Merz believed in 1989 or on what Merz meant by statements in internal Merz documents, and I fail to see how Dr. Fishman is qualified to do so.

Id. at ¶ 112 n. 6 (emphasis in original).

150. But, in my opinion, the words written by a Merz representative do not need to be "opined on". They are clear on their face. In the Merz document, Merz concluded that "[a]ll

[65] Additionally, some of the Merz documents submitted to the FDA referred to the Tempel 1989 study as treating dementia syndrome or demented patients. *See* Merz's IND at FRX-AT-02319413 (describing that in the Tempel 1989 study, "[t]wo different doses of Memantine (10mg/d or 20 mg/d) were compared for a period of nine weeks in elder patients suffering with moderate dementia" and citing Tempel 1989 in a table entitled "Tabulated other studies in dementia"); *see also id.* at FRX-AT-02319406-9407 (stating "[p]articular effects of Memantine demonstrated in clinical trials in patients suffering from dementia include as follows: . . . As compared to placebo a significant improvement in mood and depressive conditions could be demonstrated after 6 weeks of treatment. Furthermore, the inverse relationships between decreased activity during daytime and insomnia also could be improved (Tempel, 1989)" (footnote omitted)).

[66] In his deposition, Dr. Roman Gortelmeyer confirmed that OBS (organic brain syndrome) and OPS (organic psycho syndrome) are the same and that the words are interchangeable. Gortelmeyer Dep. Transcript, *Forest Labs. Inc. v. Cobalt Labs. Inc.* (October 29, 2009) ("**Gortelmeyer Dep.**") at 133:5-12.

[67] In his deposition, Dr. Gortelmeyer also confirmed that Merz prepared the English translation of the document containing the sentence cited by Dr. Fishman from a German document. Gortelmeyer Dep.at 136:14-18. He noted, however, that the original sentence in the German document used the term "and/or" rather than "or," meaning that the patients suffered from Alzheimer's disease or cerebral sclerosis or both. *Id.* at 143:5-144:7.

patients participati[ng] in the [Tempel] study suffered from organic brain syndrome . . . resulting from Alzheimer's disease or cerebral sclerosis."[68]

151. Based on the Fishman and Farlow expert opinions and, in my opinion, a reasonable and competent patent attorney would recognize that the Memantine Studies were likely to be found to disclose studies of the use of memantine to improve characteristics associated with dementia in patients. While the Memantine Studies did not disclose explicitly that these patients were diagnosed specifically with Alzheimer's Type Dementia ("**ATD**"), it is apparent from Dr. Fishman's testimony that the vast majority of patients with dementia have ATD. The statements in the Merz Memo also confirm the presence of ATD patients within the Memantine Studies.

152. As a result and in my opinion, a reasonable and competent patent attorney would recognize that the District Court was likely to find that dementia patients are a genus of patients within the Memantine Studies, and ATD patients are one species of that genus, in fact, the majority population in that genus[69].

153. Under Federal Circuit precedent, "[i]t is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus." *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006). Where, however, a genus "is so limited that a person of ordinary skill can 'at once envisage each member of this limited class,'" *In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009) (quoting *Eli Lilly and Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1376 (Fed. Cir. 2006)), "[i]n that limited circumstance, a reference describing the genus anticipates every species within the genus." *Id.* (citing *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1377 (Fed. Cir. 2005)); *see Bristol–Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1380 (Fed. Cir. 2001) (noting that "the disclosure of a small genus may anticipate the species of that genus even if the species are not themselves recited").

[68] In his deposition, Dr. Gortelmeyer also confirmed that Alzheimer's disease was not listed as an exclusion criteria in the study plan and that patients with Alzheimer's disease were not specifically excluded from the study. Gortelmeyer Dep. at 134:11-16.

[69] For example, in a 1982 article, Gabe J. Maletta, *et al.*, *Organic Mental Disorders in a Geriatric Population*, Am J. Psychiatry 139:4 (April 1982), the authors diagnosed 100 elderly patients with complaints of organic mental disorder. Of the 73 patients diagnosed with organic mental disorders, 59% were diagnosed as having primary degenerative dementia (*i.e.*, ATD), 14% were diagnosed as having multi-infarct dementia, 10% were diagnosed as having dementia associated with alcoholism, and 8% were diagnosed as having dementia associated with specific neurologic disease. *Id.* at 522. In turn, of the 69 elderly patients who fell within the group who were diagnosed with dementia, 62% (43 patients) were diagnosed with primary degenerative dementia (*i.e.*, ATD), 14% (10 patients) with multi-infarct dementia, 10% (7 patients) with dementia associated with alcoholism, and 9% (6 patients) with dementia associated with specific neurologic disease. *Id.* at 522, Table 1.

154. In my opinion, from the testimony of the experts, the size of the genus disclosed in the Memantine Studies (*i.e.*, a genus of dementia sufferers) is limited, and ATD constitutes the "vast majority" of dementia suffers falling within that genus. It is apparent that the Memantine Studies disclosure of the treatment of dementia sufferers would lead one skilled in the art to "at once envisage each member of this limited class," in particular, to envision ATD patients as members.

155. As noted above, the Memantine Studies are concerned with treating patients suffering from dementia. This is particularly true for disclosures such as the Marcea & Tempel 1988 publication which indicated that the patients selected included those that had senile dementia and presenile dementia. As reflected in the DSM-III-R, "nearly all [cases of senile and presenile dementias] are associated with histopathologic changes of Alzheimer's disease." The Tempel 1989 publication and the Merz memo also demonstrate that this conclusion is correct. The Merz memo further supports that conclusion that one skilled in the art would recognize that within the dementia genus, the species of patients treated in the Tempel 1989 publication was limited to those that suffered from Alzheimer's disease or cerebral sclerosis.

156. In my opinion, Dr. Farlow did not effectively counter the above arguments by dismissing the Merz Memo on the grounds that the publication itself did not disclose that the patients suffered from Alzheimer's disease or cerebral sclerosis. Dr. Farlow's reasoning missed the point as to the why the Merz memo was relevant and why the Tempel 1989 publication would likely be found to anticipate the asserted claims in the '703 patent. The Tempel 1989 publication illustrates that one skilled in the art would have recognized that the size of the genus of the patient population in the Memantine Studies was very small, that one skilled in the art would "at once envisage each member of this limited class" and that one skilled in the art would recognize that patients with Alzheimer's disease would be a member or species of that group.

157. In view of the forgoing and in my opinion, a reasonable and competent patent attorney would recognize that the asserted claims of the '703 patent were likely to be found to be anticipated by the Memantine Studies.

d. Conclusion

158. In my opinion, a reasonable and competent patent attorney would have realized that that Mylan had met its burden and could prevail with regard to invalidating the asserted claims of the '703 patent as being anticipated under 35 U.S.C. § 102, based upon the

above prior art. On the other hand, the '703 patent was entitled to a presumption of validity and had survived reexamination[70].

159. Taking all of the above into consideration and in my opinion, a reasonable and competent patent attorney would have determined that the chance of success was about 55% in favor of Mylan to about 45% in favor of Forest and Merz for Mylan to invalidate the asserted claims of the '703 patent as being anticipated under 35 U.S.C. § 102.

2. 35 U.S.C. § 103 – Obviousness

a. Mylan's Position

160. Mylan's position in the Namenda Litigation was that the claims of the '703 patent were invalid as obvious because a "person of ordinary skill in the art in 1989, in view of the [Memantine Studies], would have found it obvious to administer memantine to Alzheimer's disease patients because patients afflicted with Alzheimer's disease represent the largest subset of an elderly group of patients classified as having organic brain syndrome, cerebro-organic psycho-syndrome, organic mental disorder, organic brain disorder, organic dementia, or senile dementia." Pretrial Order, Exhibit 12, ¶ 134; *see also id.* at ¶¶ 119–176. Moreover, Mylan argued that there were no secondary considerations that overcame Mylan's strong showing of obviousness, and in fact the secondary considerations supported a conclusion that the claims were not patentable. *Id.* at ¶ 173.

b. Forest and Merz's Position

161. Forest and Merz's position in the Namenda Litigation was that "the claims of the '703 patent [were] not *prima facie* obvious in view of the cited art" and that "objective factors further demonstrate the nonobviousness of the '703 patent" Pretrial Order, Exhibit 12, ¶¶ 127– 96.

c. Analysis

162. With respect to the scope of the prior art, the Memantine Studies on which Mylan relied for purposes of its anticipation arguments (*i.e.*, Ambrozi & Danielczyk, Tempel (1989), Marcea & Temple, and Schafer & Thiery) each disclose orally administering memantine to live human patients. Based on these references, Mylan argued that "memantine

[70] At the same time, a reasonable and competent patent attorney would recognize that (1) the '703 patent is a Third Tier patent because the compound memantine and its use for treating other neurological conditions was admittedly in the prior art, and therefore the patent was susceptible to validity challenges; (2) foreign counterparts to the '703 patent had been revoked and/or invalidated in foreign jurisdictions; and (3) the procedures before the USPTO were *ex parte*, and thus the USPTO did not have the benefit of Mylan's arguments and evidence.

hydrochloride acts on the patient according to its naturally occurring mechanism of action." Pretrial Order, Exhibit 12, ¶ 159.

163. Forest and Merz took the position that those references did not disclose administering memantine to a "patient diagnosed with Alzheimer's disease" as required by the claim construction of the '703 patent. *See* Report, Paragraphs 129, 132.

164. Forest and Merz also argued that Mylan did not establish a *prima facie* case of obviousness because there was no reasonable expectation of success or motivation to combine the references, citing Fleischhacker *et al.* (1986) "Memantine in the treatment of senile dementia of the Alzheimer's type, *Prog. Neuro-Psychopharm. & Biol. Psychiat.* *See* Pretrial Order, Exhibit 11, ¶ 144.

165. Forest and Merz conceded that Fleischhacker "report[ed] the administration of memantine to a patient population diagnosed with a condition characterized as 'senile dementia of the Alzheimer type.'" Pretrial Order, Exhibit 11, ¶ 131. Nonetheless, Forest and Merz took the position that Fleishhacker would discourage a person of skill in the art from pursuing memantine to treat DAT. *See id.* at ¶ 127.

166. In response, Mylan could have made the following arguments regarding a "reasonable expectation of success."

167. First, during his deposition, Dr. Fleischhacker[71] testified that "if one did a longer-term study, results may have looked differently." Fleischhacker Dep. Transcript, *Forest Labs. Inc. v. Cobalt Labs. Inc.* (Sept. 9, 2009) ("**Fleischhacker Dep.**") at 34:16-36:18. Dr. Fleischhacker further agreed that his article reported inconclusive results not that memantine was ineffective in the treatment of SDAT[72]. *Id.* at 37:1-22; 254:24-257:18; 261:12-262:7. As a result, a reasonable and competent patent attorney would have recognized that the District Court would likely conclude that even taking into consideration the Fleischhacker reference, a person of ordinary skill in the art would be motivated to combine references.

168. Second, Mylan would have argued that the "the subpopulation of Alzheimer's disease patients claimed by the '703 patent is immediately envisioned by the genus disclosed in the [Memantine Studies] references." Pretrial Order, Exhibit 12, ¶ 159; *see also* Report, Paragraph 131, 134. For these reasons, a reasonable and competent patent attorney would have recognized that the court would likely conclude that a person of ordinary skill in the art would be motivated to combine references.

[71] I note that Dr. Fleischhacker was on Mylan's trial witness list. *See* Pretrial Order, Exhibit 8 at 2.

[72] Dr. Fleischhacker testified that SDAT stands for "senile dementia of the Alzheimer['s] type. Fleischhacker Dep. at 24:11-13, which has the same meaning as ATD, *see* Report, Paragraph 151, and DAT, *see* Report, Footnote 59.

169. Third, with respect to the level of skill in the art, Forest, Merz, and Mylan proposed definitions for a person of ordinary skill. Pretrial Order, Exhibit 11, ¶ 44; Pretrial Order, Exhibit 12, ¶ 172. Based on my review, the differences between the definitions appear to be insubstantial, and both definitions set forth a high level of skill. Thus, a reasonable and competent patent attorney would have recognized that the District Court would likely conclude that the high level of skill supported Mylan's argument that a person of ordinary skill in the pertinent art would have had a reasonable expectation of success.

170. For all the above reasons and in my opinion, a reasonable and competent patent attorney would recognize that Mylan presented a strong showing that the claimed subject matter was prima facie obvious under 35 U.S.C. §103.

171. However, my analysis cannot stop with Mylan establishing a prima facie case of obviousness. Secondary consideration must be considered in an obviousness analysis. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 399 (2007). However, secondary considerations, by themselves, are not dispositive of an obviousness contention. *See, e.g.*, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007); *see also Leapfrog Enters. Inc. v. Fisher-Price Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

172. In fact, with respect to secondary considerations, Mylan argued that Forest and Merz's evidence of secondary considerations would not be able to overcome Mylan's strong showing of *prima facie* obviousness. Pretrial Order, Exhibit 12, ¶¶ 173, 266.

173. Regarding secondary considerations, Forest and Merz argued that before the discoveries of the '703 patent, many others had tried and failed to meet a long-felt[73] need for safe and

---

[73] For example, Dr. Fishman, an expert for Mylan, provided the following testimony:

> Q. Did you take into account whether or not there had been a long felt need in the field for the claimed invention?
> A. I did.
> ....
> Q. How did you do so?
> A. Through my knowledge of the available drugs in 1989 for the treatment of Alzheimer's disease.
> . . . .
> Q. Okay. As of 1989 was there a need for additional and improved drugs for the treatment of Alzheimer's?
> A. Yes.

Fishman Dep. at 87:7-88:16.

> Q. In 1989, in your view, was there a lack of any proven effective treatment for dementia of the Alzheimer's type?
> A. At that time, yes.

Id. at 92:1-4.

> Q. Is Namenda the best tolerated of the Alzheimer's approved drugs right now?
> MS. STAFFORD: Objection.

effective treatments for dementia of the Alzheimer's type. Pretrial Order, Exhibit 11, ¶ 168.

174. Forest and Merz identified several secondary considerations including: (1) teaching away; (2) failure of others; (3) commercial success; (4) evidence of copying by others; and (5) acquiescence of validity. Pretrial Order, Exhibit 11, ¶¶ 168-193.

175. Forest and Merz described the Fleischhacker reference as "teaching away" from a skilled artisan using memantine as a candidate to treat dementia of the Alzheimer's type, Pretrial Order, Exhibit 11, ¶ 140, because Fleischhacker observed "'[n]o significant differences between the two groups could be calculated by statistical evaluation,'" *Id.* at ¶ 134 (quoting Fleishhacker at 89).

176. As discussed in Report, Paragraph 167, Dr. Fleischhacker's testimony showed that his article taught inconclusive results not that memantine was ineffective for treating SDAT.

177. With respect to the "failure of others", Forest and Merz's argument was based on an assumption that Fleischhacker's reference demonstrated "failure." As discussed above, a reasonable and competent patent attorney would have recognized that Fleischhacker did not reflect a "failure" and at most was "inconclusive." *See* Report, Paragraph 167.

178. With respect to commercial success, Mylan argued that Forest and Merz had not shown a nexus between Namenda and the claimed subject matter. In addition, Mylan argued that evidence of extensive marketing and advertising obscured any purported nexus between commercial success and the merits of the claimed invention. *See* Pretrial Order, Exhibit 12, ¶ 267. According to Dr. John P. Murry, Jr. Ph.D., Forest and Merz's expert on "commercial success," Namenda was, in fact, a "commercially successful product" and its "success is due to the efficacy and safety of Namenda as claimed in the '703 patent." Murry Expert Report at ¶ 70.

179. First, the '703 patent contains method of treatment claims that are directed to a method for the prevention or treatment of cerebral ischemia or to the treatment of an imbalance of neuronal stimulation after Alzheimer's disease. But, the claims are not directed to and do not contain specific language regarding efficacy and safety methods. Second, apparently, Dr. Murry was trying to use "safety and efficacy" as a "bridge" or nexus to connect any

---

THE WITNESS. Yes. Sorry.

Id. at 95:17-20.

Q. In your opinion today, is there or is there not still a need for improved drugs for the treatment of Alzheimer's disease?
A. Yes there is.

Id. at 143:21-24.

alleged commercial success with the claimed methods. (*i.e.*, commercial success → safety and efficacy → method claims). But, there is no live human data present in the '703 patent to demonstrate safety and efficacy of Namenda that might create the "bridge" or alleged nexus with the claims. Third, if Mylan were correct that its generic Namenda product did not infringe the asserted claims, then it was also correct that Forest and Merz could not show a nexus between the claimed subject matter and Namenda.

180. With respect to "copying by others," Forest and Merz relied on evidence of copying by the Generic Companies in their ANDAs. Pretrial Order, Exhibit 11, ¶ 190. In response, Mylan cited cases establishing that copying in the Hatch-Waxman context provides "little weight" of nonobviousness. Pretrial Order, Exhibit 12, ¶ 268 (citing *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995); *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 642 F. Supp. 2d 329, 373 (D. Del. 2009), aff'd *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 Fed. App'x 978 (Fed. Cir. 2010); *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, No. IP 99-38-C H/K, 2001 WL 1397304, at *14 (S.D. Ind. Oct. 29, 2001)).

181. With respect to acquiescence to validity, apparently Forest and Merz intended to present evidence that the other Generic Companies who settled with Forest and Merz had acknowledged the validity of the '703 patent in the context of resolving their Namenda Litigation. First, my review of the record does not show such "acknowledgement."[74] Second, if such acknowledgements were present, based on my experience with Hatch-Waxman litigation settlements, it is common for a generic defendant to be asked by the brand company to acknowledge the validity of a patent in question.

182. However, the main goal of a generic company is to negotiate a patent license under terms which it perceives are reasonable from a business viewpoint so the generic company can sell its generic equivalent product. Whether or not a generic defendant acknowledges the validity of a patent would have little, if any, impact on the sales of its generic product. As a result, it would be a relatively easy for a generic company to accept acknowledgement of a patent. For this reason, a reasonable and competent patent attorney would recognize that the District Court would have placed limited weight on other generic companies accepting patent validity in a Hatch-Waxman settlement agreement.

---

[74] *See* Settlement Agreement between Forest, Merz, and Dr. Reddy's (FRX-AT-00000001-037); *see also* Settlement Agreement between Forest, Merz, and Cobalt (FRX-AT-00000038-061); *see also* Settlement Agreement between Forest, Merz, and Sun (FRX-AT-00000112-147); *see also* Settlement Agreement between Forest, Merz, and Upsher-Smith (FRX-AT-00000148-183); *see also* Settlement Agreement between Forest, Merz, and Teva (FRX-AT-00000184-217); *see also* Settlement Agreement between Forest, Merz, and Amneal (FRX-AT-00000218-252); *see also* Settlement Agreement between Forest, Merz, and Apotex (FRX-AT-00000274-298); *see also* Settlement Agreement between Forest, Merz, and Lupin (FRX-AT-00000340-362); *see also* Settlement Agreement between Forest, Merz, Orgenus, and Orchid (FRX-AT-00000380-402); *see also* Settlement Agreement between Forest, Merz, and Wockhardt (FRX-AT-01710237-272).

d. Conclusion

183. In my opinion, a reasonable and competent patent attorney would have recognized that even if Mylan did not prevail with its anticipation defense, Mylan presented a strong showing that the claimed subject matter was prima facie obvious.

184. In my opinion, the Memantine Studies describe successful oral administration of memantine to an elderly patient population suffering from dementia and OBS. To the extent that Forest and Merz may have argued that these four references do not expressly use the words "Alzheimer's disease" to describe the patients' diagnosis, this conclusion would have been obvious to a skilled artisan, for example in view of the Fleischhacker reference. Once this *prima facie* case of obviousness was established, a reasonable and competent patent attorney would have recognized that it would be difficult for Forest and Merz to overcome this *prima facie* case of obviousness through secondary indicia evidence.

185. On the other hand, Forest and Merz's arguments on secondary considerations were not insignificant. Secondary considerations, however, tend not to overcome cases involving a strong showing of prima facie obviousness. Nevertheless, I note that Mylan did not present a strong rebuttal to Forest and Merz's arguments on secondary considerations in its proposed findings of fact and conclusions of law[75]. *See, e.g.*, Pretrial Order, Exhibit 12, ¶¶ 173–176, 276–269.

186. In my opinion, a reasonable and competent patent attorney therefore would have recognized that the District Court's conclusion on obviousness would have come down to deciding if Mylan's showing on prima facie obviousness was sufficiently strong to counter Forest and Merz's arguments on secondary considerations.

187. Taking all of the above into consideration and in my opinion, a reasonable and competent patent attorney would have realized that the chance of success was about 45% in favor of Mylan to about 55% in favor of Forest and Merz for Mylan to invalidate the asserted claims of the '703 patent as being obvious under 35 U.S.C. § 103 based on the prior art.

3. 35 U.S.C. § 112 – Enablement

188. To comply with the enablement requirement of 35 U.S.C. § 112, ¶ 1, a patent specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561, (Fed. Cir. 1993); *see also Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1339–40 (Fed. Cir. 2003) (quoting *Genentech, Inc.*, 108 F.3d at 1365).

[75] While Mylan would have had the opportunity to present a more substantial rebuttal at trial, my estimate is based on the conservative assumption that Mylan's rebuttal evidence would not be substantial.

189. Enablement is "closely related" to the requirement of § 101 utility. As the Federal Circuit has articulated, "[i]f a patent claim fails to meet the utility requirement because it is not useful or operative, then it *also* fails to meet the how-to-use aspect of the enablement requirement." *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1358 (Fed. Cir. 1999) (emphasis added); *see also* M.P.E.P. § 2164.01(c) (providing that "[i]f a statement of utility in the specification contains within it a combination of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. § 112 is satisfied").

190. The standard for what constitutes proper enablement under 35 U.S.C. § 112 differs from the standard for what constitutes proper enablement for purposes of anticipation by a prior art reference under § 102. This is because 35 U.S.C. § 112 "provides that the specification must enable one skilled in the art to 'use' the invention whereas [section] 102 makes no such requirement as to an anticipatory disclosure." *In re Hafner*, 410 F.2d at 1405 (C.C.P.A. 1969).

191. Enablement is a question of law based on underlying factual inquiries. *Genentech*, 108 F.3d at 1368.

192. In the Namenda Litigation, Mylan bore the burden of establishing that the '703 patent claims did not meet the requirements of 35 U.S.C. § 112 by clear and convincing evidence. *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1359 (Fed. Cir. 1998); *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1369 (Fed. Cir. 2009); *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001).

a. An Unproven Hypothesis Is Not Enough (Mechanism of Action)

(1) Mylan's Position

193. Mylan's position in the Namenda Litigation was that fact and expert witness testimony established that the '703 patent specification would not have enabled one of ordinary skill in the art to make and use the claimed invention. Mylan argued that although the specification disclosed that certain compounds (*i.e.*, memantine and other adamantane derivatives) exhibit a particular pharmacological activity (*i.e.*, NMDA receptor antagonism), it did not demonstrate that those compounds are effective in treating patients diagnosed with Alzheimer's disease and thus how to use such compounds. *See, e.g.*, Pretrial Order, Exhibit 12, ¶¶ 177–87.

(2) Forest and Merz's Position

194. Forest and Merz's position in the Namenda Litigation was that a person of ordinary skill in the art reading the '703 patent at the relevant time would have known that one of the proposed mechanisms underlying Alzheimer's disease was a pathophysiological situation in which excessive inflow of calcium through NMDA receptor channels destroys neurons in particular areas of the brain. Accordingly, Forest and Merz, argued that a person of ordinary skill in the art reading the '703 patent at the relevant time would have known that partial blockade of NMDA receptors could prevent pathophysiological conditions while permitting long-term potentiation, and thus how to use the adamantane derivatives. *See, e.g.*, Pretrial Order, Exhibit 11, ¶¶ 197–231, 383–84.

(3) Analysis[76]

195. In my opinion and based on the Expert Reports, a reasonable and competent patent attorney was likely to conclude that the '703 patent would be found to propose an unproven *hypothesis* that because memantine exhibits activity as an NMDA antagonist, it *may* be useful in treating Alzheimer's disease. Such disclosure was likely to be found legally insufficient to teach a skilled artisan how to use the '703 patent method of treatment claims under 35 U.S.C. § 112.

196. In support of its position,[77] Mylan argued that the '703 patent failed to provide any example in which an adamantane derivative was used to treat a patient diagnosed with Alzheimer's disease, either by preventing or treating cerebral ischemia, treating an imbalance of neuronal stimulation, or preventing or treating Alzheimer's disease per se.

197. Mylan relied on the expert opinion testimony of Dr. David A. Greenberg, M.D., Ph.D., who concluded that "the '703 patent would have taught one of ordinary skill in the art that . . . the claimed adamant[a]ne derivatives, including memantine, would not have been reasonably expected to be beneficial to patients diagnosed with Alzheimer's disease . . ." at the relevant time[78, 79]. Greenberg Report at ¶ 12. In rebuttal, Forest and Merz relied on

[76] For a more detailed discussion of the applicable law, see Exhibit M.

[77] S*ee* Pretrial Order, Exhibit 12, ¶¶ 178–82.

[78] In his Expert Report, Dr Greenberg (Mylan's Expert) referenced April 14, 1989 as the relevant time (*i.e.*, the foreign application priority date). Greenberg Report at ¶ 4. However, during his Deposition, Dr. Greenberg noted that his Report needed to be corrected, and that the relevant time should have been the filing date of the '703 patent (*i.e.*, April 11, 1990). Greenberg Dep. Transcript, *Forest Labs Inc. v. Cobalt Labs. Inc.* (Feb. 18, 2010) ("**Greenberg Dep.**"), 15:13-18:14. He further explained that if one were to substitute in his Report the April 1990 date for the April 1989 date, the analysis in his Report would not change in any way. *Id.* at 18:4-13.

[79] It seemed that Forest and Merz also were under the impression and, in fact, admitted that the relevant time to determine enablement was at the priority date – April 1989, rather than the April 1990 filing date of the '703 patent. In the Pretrial Order, Forest and Merz stated:

the expert opinion testimony of Dr. Roberto Malinow, M.D., Ph.D., who concluded that the claims of the '703 patent were enabled based on the experiments in the specification. Malinow Opposition Report at ¶ 19[80].

198. The dispute between the experts was whether the *in vitro*[81] and *in vivo* tests[82], which both experts agree show that memantine exhibits activity as an NMDA antagonist, were sufficient to teach one skilled in the art that memantine could be used as an NMDA antagonist to treat patients diagnosed with Alzheimer's disease.

199. With respect to the *in vitro* tests disclosed in the '703 patent, Dr. Greenberg opined that the "*in vitro* tests show that memantine works by blocking NMDA receptors or channels." Greenberg Report at ¶ 15. Dr. Malinow agreed with this assessment. Malinow Opposition Report at ¶ 58. Dr. Greenberg further opined that at the relevant time, such test results would "not provide one of ordinary skill in the art with a reasonable expectation that administering memantine to patients diagnosed with Alzheimer's disease would be beneficial and do not overcome the reasonable expectation that such administration would have further impaired the patients." Greenberg Report at ¶ 15.

> 4. Whether Mylan can prove by clear and convincing evidence that any single alleged prior art reference (1) discloses each and every element, either expressly or inherently, of any asserted claim of the '703 patent, and (2) does so in a way that would enable a person of ordinary skill in the art to practice the claimed invention without undue experimentation as of April 14, 1989.
>
> . . . .
>
> 6. Whether, as of April 14, 1989, the specification of the '703 patent adequately disclosed to a person of ordinary skill in the art how to practice any of the asserted claims of the '703 patent without undue experimentation.

Pretrial Order, Exhibit 3, Section II.A., ¶¶ 4,6; *see also* Pretrial Order, Exhibit 11, ¶¶ 197-231; *see also* Malinow Opposition Report; *see also* Farlow Opposition Report.

[80] During his deposition, Dr. Malinow was asked about the enablement of the method of treatment claims of the '703 patent. Specifically, he was asked if there was a specific example (*e.g.*, experiment) described in the '703 patent where memantine had been orally administered to a human diagnosed with Alzheimer's disease. He answered as follows:

> Well, again, there was this example of tablets that I assume was meant for humans. There was memantine acting on human brain tissue. And there was the mention of cerebral ischemia in underlying Alzheimer's disease. So I think if you put those together, you can call that an example.

Malinow Dep. Transcript, *Forest Labs. Inc. v. Cobalt Labs. Inc.* (Jan. 26, 2010) ("**Malinow Dep.**"), 161:11-23.

[81] Experiments A, B, and G of the '703 patent.

[82] Experiments C, E, and F of the '703 patent.

200. Dr. Malinow, however, disputed this contention. According to Dr. Malinow, "the patent discloses that ***overactivation*** of NMDA receptors allows excessive influx of calcium into the neuron, eventually leading to cell death." Malinow Opposition Report at ¶ 52 (emphasis in original). Dr. Malinow opined further that "[a] person of ordinary skill in the art on April 14, 1989 reading the '703 patent disclosure would have known that patients diagnosed with Alzheimer's disease *may* suffer from overactivated NMDA receptors leading to 'degeneration and loss of nerve cells.'" *Id.* (emphasis added) (quoting '703 patent at 3:3-17). And, Dr. Malinow opined, that "partial blockade of NMDA receptors could prevent pathophysiological conditions while permitting LTP."[83] *Id.* at ¶ 53 (citing R. Schwarcz & B. Meldrum, *Excitatotry amino acid antagonists provide a therapeutic approach to neurological disorders*, Lancet 2(8447): 140-3 (Jul. 20, 1985)). According to Dr. Malinow, LTP "is thought to be responsible for the formation and retention of memory,"[84] *id.* at ¶ 34, and, "[l]oss of synapses and dysfunction of LTP is thought to contribute to [learning and memory cognitive] deficits" from which patients diagnosed with Alzheimer's disease suffer. *Id.* at ¶ 36.

201. In other words, Dr. Malinow asserted that the '703 patent states an unproven *hypothesis* that an NMDA antagonist that creates partial blockade of the NMDA receptors may be used to treat patients with Alzheimer's disease. Based on my review of his report, Dr. Malinow cited to no other evidence – beyond the hypothetical – showing that one skilled in the art would understand that the *in vitro* tests were correlated to or indicative of an ability to treat Alzheimer's disease in diagnosed patients. Dr. Malinow cited to no evidence – beyond the hypothetical – showing that one skilled in the art would understand how to achieve partial blockage of NMDA receptors at the relevant time.

202. With respect to the three *in vivo* animal tests in the specification[85], Dr. Greenberg explained that the "Anticonvulsant Effect" test of Experiment C was recognized as relating to "the treatment of seizures (epilepsy)," that the "Protection Against Cerebral

---

[83] During his deposition, however, Dr. Malinow was not able to confirm that Schwarcz used the term "partial blockade." Malinow Dep. at 206:4-24. Dr. Malinow was also unable to identify any reference cited in his expert report actually showing an assay that establishes that partial blockade of NMDA receptors was achieved. He testified that he assumed that the Schwarcz article would be "sufficient reference." *Id.* at 233:3-21.

[84] In his deposition, Dr. Malinow explained the importance of permitting only partial blockade of the NMDA receptors. Dr. Malinow testified that, "NMDA receptors participate in an important role in learning." Malinow Dep. at 206:15-16. Dr. Malinow testified further that "you don't want to completely block the NMDA receptors, because if you did, then you would block learning." *Id.* at 206:18-20.

Dr. Malinow, however, was unable to identify a single reference cited in his Report that showed at the relevant time an assay establishing partial blockade of NMDA receptors, that permitted long term potentiation (LTP) but prevented pathophysiological conditions of overstimulation of those receptors. *See, e.g., id.* at 233:3-23.

[85] Experiments C, E, and F of the '703 patent.

Ischemia" test of Experiment E was recognized as relating to "transient forebrain ischemia (brain damage following cardiac arrest)," and that the "Protection Against NMDA-Induced Mortality" test of Experiment F was recognized as relating to "NMDA overdose." Greenberg Report at ¶ 16.

203. Dr. Greenberg further indicated that the "Anticonvulsant Effect" test of Experiment C would not be viewed as relevant to the treatment of Alzheimer's disease at the relevant time because "seizures were known to be uncommon in Alzheimer's disease, and the ability of a drug to prevent seizures could not be reasonably correlated with efficacy in treating Alzheimer's disease." *Id.*

204. Dr. Greenberg also opined that the "Protection Against Cerebral Ischemia" test of Experiment E was recognized as corresponding "most closely to cardiac arrest in humans, and is not plausibly related to Alzheimer's disease." *Id.* Dr. Greenberg further noted that the "method cited in [Experiment E] is that of Smith et al. (1982), who described their method as one designed to reduce cerebral blood flow, and made no mention of Alzheimer's disease." *Id.*

205. Finally, with respect to the "Protection Against NMDA-Induced Mortality" test of Experiment F, Dr. Greenberg noted that this test involved "using a drug to prevent the death of mice given an intraperitoneal injection of a large dose of NMDA." *Id.* Dr. Greenberg observed that the '703 patent "cited the method of Leander et al. (1984), but that paper [neither] identif[ied] the cause of death in NMDA-treated mice nor did it mention Alzheimer's disease." [86] *Id.*

206. Dr. Greenberg also noted that at the relevant time, although no fully satisfactory animal models of Alzheimer's disease[87] existed, several possibly relevant animal models were recognized. *Id.* at ¶ 14. However, the '703 patent did not report any results using those models. *Id.*

207. In response, Dr. Malinow did not dispute that the animal models cited by Dr. Greenberg were recognized as relevant to Alzheimer's disease and that the '703 patent did not disclose results employing those models. Malinow Opposition Report at ¶ 66. Dr. Malinow, however, cited to Experiment E ("Protection Against Cerebral Ischemia") which reports "the results of an animal model that induces pathophysiological conditions

[86] During his deposition, Dr. Greenberg confirmed his position that the *in vivo* test disclosed in Experiment F was unrelated to Alzheimer's disease. Regarding what a person of ordinary skill in the art who was reading Experiment F would had thought to be the cause of the death in the mice who were treated with NMDA, Dr. Greenberg stated "I think they would probably . . . think that seizures were a likely cause of death . . . . [C]ertainly, mice have seizures, and that's what I think most people would have assumed killed them." Greenberg Dep. at 89:8-90:1-3.

[87] *See* Greenberg Dep. at 66:3-12.

that are *thought* to occur in Alzheimer's disease." *Id.* (emphasis added). Dr. Malinow, however, did not offer any other evidence showing that one skilled in the art would have such understanding of Experiment E, at the relevant time. *Id.*

208. Moreover, Dr. Malinow did not dispute that the method cited in Experiment E of the '703 patent was "designed to reduce cerebral blood flow, and made no mention of Alzheimer's disease" as observed by Dr. Greenberg. *Id.* Instead, Dr. Malinow cited to an unproven *hypothesis* articulated in the '703 patent itself and to "subsequent work" after the filing date of the '703 patent[88]. *Id.* at ¶¶ 66–67.

209. In effect, Dr. Malinow's position was that the *in vivo* and *in vitro* tests of the '703 patent enabled one skilled in the art to use memantine to treat Alzheimer's disease because these tests showed that memantine exhibited activity as a NMDA antagonist and that the pathological activation of NMDA receptors can create pathophysiological conditions "*thought* to contribute to [learning and memory] deficits" underlying Alzheimer's disease. *Id.* at ¶¶ 35–36 (emphasis added).

210. In support of his above position, Dr. Malinow cited to papers that were published after the relevant date. *Id.* at ¶¶ 36–37. Namely, Dr. Malinow relied upon the following articles that were published after the foreign priority date of the '703 patent and after the U.S. filing date of the '703 patent:

- F. Kamenetz, *et al.*, *APP processing and synaptic function*, Neuron 37(6): 925-37 (Mar. 27, 2003);
- G.M. Shankar, *et al.*, *Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway*, J. Neuroscience 27(11): 2866-75 (Mar. 14, 2007);
- W. Wei, *et al.*, *Amyloid-beta from axons and dendrites reduces local spine number and plasticity*, Nature Neuroscience (in press)[89];
- M.P. Mattson, *et al.*, *b-Amyloid peptides destabilize calcium homeostasis and render human cortical neurons vulnerable to excitotoxicity*, J. Neurosci. 12: 376-89 (1992);
- R. Tremblay, *et al.*, *Transient NMDA-receptor inactivation provides long-term protection to cultured cortical neurons from a variety of death signals*, J. Neurosci. 20: 7183-92 (2000);

[88] Based on the above evidence cited by Dr. Malinow, it is apparent that this hypothesis was not established until after the '703 patent was filed.

[89] The Wei publication was in press at the time Dr. Malinow authored his report (December 18, 2009) and was published online on December 27, 2009 and in the February 2010 print edition of *Nature Neuroscience*.

- A.M. Floden, *b-Amyloid stimulated microglia induce neuron death via synergistic stimulation of tumor necrosis factor and NMDA receptors*, J. Neurosci. 25: 2566-75 (2005);

- T. Harkany, *et al.*, b-*Amyloid neurotoxicity is mediated by a glutamate- triggered excitotoxic cascade in rat nucleus basalis*, Eur. J. Neurosci. 12: 2735-45 (2000);

- J.J. Miguel-Hidalgo, *et al.*, *Neuroprotection by memantine against neurodegeneration induced by b- amyloid 1-40*, Brain Res. 958: 210-21 (2002); and

- M.S. Song, *et al.*, *Memantine Protects Rat Cortical Cultured Neurons Against Beta-Amyloid-Induced Toxicity by Attenuating Tau Phosphorylation*, 28(10) Eur. J. Neurosci. 1989-2002 (Nov. 2008).

Id. at ¶¶ 36–37.

211. In my opinion, the above publications should not be considered for purposes of enablement because they were published after filing of the '703 patent. *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1324 (Fed. Cir. 2005).

212. Dr. Malinow, also cited to two additional articles that were published prior to both the foreign priority date of the '703 patent and the US filing date of the '703 patent:

- R. Schwarcz & B. Meldrum, *Excitatory amino acid antagonists provide a therapeutic approach to neurological disorders*, Lancet 2(8447): 140-3 (Jul. 20, 1985); and

- P.L. Ornstein, *et al.*, *Synthesis and pharmacology of a series of 3- and 4-(phosphonoalkyl)pyridine- and -piperidine- 2-carboxylic acids: Potent N-methyl-D-aspartate receptor antagonists*, J. Med. Chem. 32(4): 827-33 (Apr. 1989).

Id. at ¶ 45.

213. In my opinion, the Schwarcz and Ornstein articles presented unproven *hypotheses*, but there is no evidence showing that the hypotheses were accepted by one skilled in the art at the relevant time.

214. The 1985 Schwarcz article suggested the unproven hypothesis that:

> [e]xcessive excitation by neurotransmitters can cause the death of neurons. This excitotoxic action *may* be responsible for neuronal loss in stroke, cerebral palsy, epilepsy, ageing and Alzheimer's disease, Huntington's disease, and other chronic degenerative disorders.

Schwarcz at 140 (emphasis added).

215. Granted, the Schwarcz article suggests that there *may* be a link between "excessive excitation by neurotransmitters" and neuronal loss associated with a number of diseases. The Schwarcz article however, does not claim that a skilled artisan would conclude that a link had been *established*, that neuronal receptor antagonists can be used to successfully treat Alzheimer's disease, or that an NMDA antagonist, specifically, can be used to successfully treat Alzheimer's disease. While the Schwarcz article proposed a *hypothesis*, there is no evidence showing that the Schwarcz hypothesis was accepted by one skilled in the art at the relevant time.

216. The 1989 Ornstein article suggested the hypothesis that:

> NMDA antagonists *may* prove to be useful therapeutic agents, for instance, as anticonvulsants, in the treatment of neurodegenerative disorders such as Alzheimer's disease and in the prevention of neuronal damage that occurs during cerebral ischemia.

Ornstein at 827 (emphasis added).

217. Once again, Ornstein, like Schwarcz, presented the unproven *hypothesis* that NMDA antagonists *may* prove to be useful therapeutic agents. However, Ornstein does not purport to *establish* such link. And, like Schwarcz, there is no evidence demonstrating that this hypothesis was accepted by one skilled in the art at the relevant time.

218. Dr. Malinow appeared to concede that one skilled in the art would not consider such possible link to be "conclusive." Malinow Opposition Report at ¶ 45. Dr. Malinow also appeared to concede that the preclinical evidence had only "suggest[ed] certain mechanisms . . . ." *Id.*

219. Further, Dr. Malinow seemed not to dispute Dr. Greenberg's position that the prevailing view at the relevant time was that NMDA antagonists would not be considered beneficial for the treatment Alzheimer's disease.

220. As Dr. Greenberg stated in his Report[90]:

> [m]emory loss is the most characteristic clinical feature of Alzheimer's disease. At the time the '703 patent was filed,

[90] During his deposition, Dr. Greenberg noted that there was a possible concern with respect to known NMDA antagonists regarding "the implication of NMDA systems in long-term potentiation and consequently memory. Greenberg Dep. at 75:11-13. Also, Dr. Greenberg testified that NMDA antagonists included drugs like phenacyclamine ("**PCP**"), angel dust, and ketamine that were known to cause memory disturbance or psychosis. *Id.* at 76:25-77:14.

> memory formation was thought to involve a cellular process called long-term potentiation (LTP), which depended on the activity of NMDA receptors and *was inhibited by NMDA blockers*. At the time the '703 patent was filed, several studies had shown evidence for a deficiency in NMDA receptor-mediated neuronal transmission in the brains of patients with Alzheimer's disease, including decreased levels of excitatory amino acid neurotransmitters and of NMDA receptors.

Greenberg Report at ¶ 13 (emphasis added).

221. Instead of disputing Dr. Greenberg's opinion, Dr. Malinow pointed to the specification of the '703 patent to show that a different hypothesis was being proposed. Malinow Opposition Report at ¶ 52. However, simply because the inventors of the '703 patent proposed an alternative hypothesis does not mean that one skilled in the art would depart from the prevailing view identified by Dr. Greenberg.

222. Dr. Malinow, also cited to two articles that were published after the foreign priority date of the '703 patent but before the US filing date of the '703 patent[91]:

- M.P. Mattson & S.B. Kater, *Development and selective neurodegeneration in cell cultures from different hippocampal regions,* Brain Res. 490(1): 110-25 (Jun. 19, 1989); and

- B.C. Rogers & H.A. Tilson, *MK-801 prevents cognitive and behavioral deficits produced by NMDA receptor overstimulation in the rat hippocampus,* Toxicol. Appl. Pharmacol. 99(3): 445-53 (Jul. 1989).

Id. at ¶ 45.

223. The two articles presented unproven *hypotheses*, but there was no evidence showing that the hypotheses were accepted by one skilled in the art at the relevant time. In other words, neither of these articles demonstrated that a NMDA antagonist could be used to treat Alzheimer's disease. Neither of these publications presented evidence showing that the hypothesis was accepted by one skilled in the art at the relevant time.

224. The Mattson 1989 article suggested the unproven hypothesis that:

> *If* glutamate is involved in the selective loss of hippocampal pyramidal neurons that occurs in disorders such as Alzheimer's disease, epilepsy, and stroke then treatments targeted at reducing

[91] In my opinion, these articles would also be irrelevant to the Namenda Litigation because Forest and Merz admitted that enablement is determined as of the priority date (*i.e.*, April 1989) rather than the filing date of the '703 patent (*i.e.*, April 1990). These publications are dated after the foreign priority date of the '703 patent. *See* Report, Footnote 79.

> glutamate receptor activation, electrical activity and calcium influx *may* prove useful in preventing neurodegeneration.

Mattson at 123, first column (emphasis added) (footnotes omitted).

225. Simply put, the Mattson article presented an unproven *hypothesis* that if glutamate is involved in Alzheimer's disease then reducing glutamate receptor activation *may* prove to be useful. However, Mattson did not purport to *establish* such link. There is no evidence demonstrating that this hypothesis was accepted by one skilled in the art at the relevant time.

226. The 1989 Rogers article started with the premise or unproven hypothesis that:

> The overstimulation of receptors for L-glutamate, particularly those of the *N*-methyl-D-aspartate (NMDA) type, has been *suggested* to play a role in mediating damage in a variety of neurodegenerative conditions or disorders ranging from ischemia/hypoxia to senile dementia of the Alzheimer's type (SDAT).

Rogers at 445, Abstract (emphasis added).

227. Rogers further explained that:

> Since evidence suggests the overactivation of NMDA receptors *may* be associated with neuronal death, there has been an increased interest in the *possible* therapeutic value of NMDA antagonists.

Id. at 445, second column (emphasis added).

228. The research presented in the Rogers article then focused on whether compound MK-801 prevented "NMDA-induced cell loss and neurobehavioral impairment." *Id.* at 446, first column.

229. The Rogers article never affirmatively concluded that an NMDA antagonist could be used to treat Alzheimer's disease. The Rogers article did not purport to *establish* such link. There is no evidence demonstrating that this hypothesis was accepted by one skilled in the art at the relevant time.

230. Two cases involving the enablement of method of treatment claims are instructive: *Rasmusson, v. SmithKline Beecham Corp.*, 413 F.3d 1318 (Fed. Cir. 2005) and *In re '318 Patent Infringement Litigation*, 578 F. Supp. 2d 711 (D. Del. 2008), *aff'd* 583 F.3d 1317 (Fed. Cir. 2009).

231. In *Rasmusson*, the Federal Circuit considered whether knowing that finasteride was a selective 5αR inhibitor was sufficient to enable one skilled in the art to use finasteride to treat prostate cancer. 413 F.3d at 1323. The Federal Circuit found that it was not. *Id.* at 1325. The Federal Circuit noted the evidence that predated the filing of the relevant patent application showed one skilled in the art would be uncertain as to whether 5αR inhibitors had anti-tumor effects. *Id.* at 1324. The Federal Circuit also noted that the other evidence presented by the patentee was unavailing for enablement purposes because it was "dated too late." *Id.*

232. The Federal Circuit further noted that while a patentee's hypothesis may be ultimately proven correct, that is not sufficient to satisfy the enablement requirement. *Id.* at 1325. Specifically, the court reasoned:

> [a]s we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that *the inventor enable an invention rather than merely proposing an unproved hypothesis*.

Id. (emphasis added).

233. Similarly, in *In re '318 Patent Infringement Litigation*, Judge Robinson from the District of Delaware considered whether claims directed to the use of glanthamine to treat Alzheimer's disease were enabled when the inventor had not performed any animal studies to test her hypothesis before filing the patent application. 578 F. Supp. 2d at 734–37. As in *Rasmusson*, the court found that despite the inventor ultimately being correct and having the hypothesis proven by subsequent testing, that evidence was not sufficient to satisfy the enablement requirement. *Id.* at 736–37.

234. On appeal, the Federal Circuit concluded that the district judge had properly held that testing done after the filing of the application "could not be used to establish enablement." *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1325 (Fed. Cir. 2009). While the testing of galantamine, a known compound, showed that it had activity, this knowledge "did not establish galantamine's utility in treating Alzheimer's disease." *Id.* at 1325–26. The Federal Circuit concluded:

> at the end of the day, the specification, even read in the light of the knowledge of those skilled in the art, does no more than state a

> *hypothesis* and propose testing to determine the accuracy of that hypothesis. That is not sufficient.

Id. at 1327 (emphasis added).

235. Such is the case regarding the method of treatment claims of the '703 patent. It is apparent from the testimony of Drs. Greenberg and Malinow that the inventors of the '703 patent included an *unproven hypothesis* in the specification of the '703 patent that since memantine exhibits activity as an NMDA antagonist, it *may* be useful in treating Alzheimer's disease[92]. The '703 patent did not prove that hypothesis by the experiments conducted, but only showed that memantine was an NMDA antagonist.

236. Moreover, based on the evidence presented, the link between an NMDA antagonist being useful in the treatment of Alzheimer's disease was not established, if at all, until after the '703 patent was filed.

237. Under those circumstances and the holdings of *Rasmusson* and *In re '318 Patent Infringement Litigation*, in my opinion the '703 patent did not enable one skilled in the art how to use the method of treatment claims to treat Alzheimer's disease using memantine[93].

(4) Conclusion

238. In my opinion, a reasonable and competent patent attorney would have realized that Mylan would have met its burden and would more likely than not prevail with regard to invalidating the claims of the '703 patent as not being enabled under 35 U.S.C. § 112, ¶

---

[92] Forest admitted as much in the original Namenda package insert approved with NDA 021487 on October 16, 2003. The original package insert states in part:

> [p]ersistent activation of central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been ***hypothesized*** to contribute to the symptomatology of Alzheimer's disease. Memantine is ***postulated*** to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist which binds preferentially to the NMDA receptor-operated cation channels. There is no evidence that memantine prevents or slows neurodegeneration in patients with Alzheimer's disease.

Namenda Approved Labeling, Oct. 16, 2013, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-487_Namenda_Prntlbl.pdf (last visited July 18, 2017), at 1 (emphasis added).

[93] During his deposition, Dr. Greenberg acknowledged that he did not consider whether a person of ordinary skill in the art would be able to perform the methods recited in the claims of the '703 patent without the use of undue experimentation. Greenberg Dep. at 54:18-25. However, in Section XI.B.3.b., below, I address "undue experimentation' as related to the claims of the '703 patent and its specification. *See* Report, Paragraphs 262-278.

1, based upon disclosing an unproven hypothesis. Simply put, the District Court would have concluded that stating a hypothesis in the patent specification would not be enough to teach a skilled artisan at the relevant time how to use the method of treatment claims of the '703 patent.

239. Taking all of the above into consideration and in my opinion, a reasonable and competent patent attorney would have realized that the chance of success was about 60% in favor of Mylan to about 40% in favor of Forest and Merz for Mylan to invalidate the claims of the '703 patent for lack of enablement under 35 U.S.C. § 112 based on the unproven hypothesis argument.

b. Breadth of "Effective Amount"

(1) Mylan's Position

240. Mylan's position during the Namenda Litigation was that the '703 patent specification would not have enabled one of ordinary skill in the art to use the *full scope* of the alleged invention. For example, the specification does not enable the entire "effective amount"[94] (*i.e.*, "from about 0.01 to 100 mg/kg") of an adamantane derivative to treat patients diagnosed with Alzheimer's disease. *See, e.g.*, Pretrial Order, Exhibit 12, ¶¶ 177–82.

(2) Forest and Merz' Position

241. Forest and Merz's position during the Namenda Litigation was that the '703 patent specification adequately disclosed to a person of ordinary skill in the art at the relevant time how to practice the full scope of the asserted claims without undue experimentation. In support of this position, Forest and Merz pointed to the experiments and examples described in the specification of the '703 patent. *See, e.g.*, Pretrial Order, Exhibit 11, ¶¶ 197–231, 383–84.

(3) Analysis[95]

242. The asserted claims of the '703 patent require an "effective amount" of an adamantane derivative to be administered for "the prevention or treatment of cerebral ischemia," "the treatment of cerebral ischemia," or for "the treatment of an imbalance of neuronal stimulation after Alzheimer's disease" in a "patient diagnosed with Alzheimer's disease."

[94] The District Court construed this term to mean "an amount shown to cause improvement, in comparison to placebo." *Forest Labs. Inc.*, 2009 WL 3010837, at *4.

[95] For a more detailed discussion of the applicable law, see Exhibit M.

243. In my opinion, the '703 patent was not enabled because of the breadth of the claimed term "effective amount."

244. Questions of enablement are evaluated against the claimed subject matter. The focus of the inquiry should be whether the full scope of the claim is enabled. Accordingly, the first analytical step requires determining exactly what subject matter is encompassed by the claims. *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1241 (Fed. Cir. 2003).

245. Claims 10, 16, and 19 of the '703 patent, which depend from independent claims 1, 14, and 17, respectively, recite that the "effective amount" of the adamantane derivative is "from about 0.01 to 100 mg/kg."

246. It is axiomatic that a dependent claim cannot be broader than the claim from which it depends[96]. *Intamin Ltd. v. Magnetar Techs., Corp.*, 483 F.3d 1328, 1335 (Fed. Cir. 2007) (noting that "[a]n independent claim impliedly embraces *more subject matter* than its narrower dependent claim" (emphasis added)); *AK Steel Corp*, 344 F.3d at 1242 (providing that "[u]nder the doctrine of claim differentiation, dependent claims are presumed to be of narrower scope than the independent claims from which they depend"). Furthermore, because a dependent claim narrows the claim from which it depends, it must "incorporate . . . all the limitations of the claim to which it refers." 35 U.S.C. § 112, ¶ 4.

247. As a result, the dose range recited in dependent claims 10, 16, and 19 must necessarily meet the limitations of their respective independent claims for administering an "effective amount" to a patient diagnosed with Alzheimer's disease. This is seen from the express language of independent claims 1, 14, and 17 regarding "effective amount." It is also supported by the statement in the specification that: "The compounds of formula 1 [adamantane derivatives] are administered in suitable form in doses ranging from about 0.01 to 100 mg/kg." '703 patent, 4:38-40.

248. Because dependent claims 10, 16, and 19 set forth a broad dose range ("from about 0.01 to 100 mg/kg") for an "effective amount," that range, at a minimum, must be included in independent claims 1, 14, and 17, respectively, whatever their limitations. The patent then must teach a skilled artisan how to practice the claimed invention along the *entire* claimed dose range, without "undue experimentation." *See, e.g.*, *In re Wright*, 999 F.2d at 1561. Thus, the specifically claimed high dose (in mg/kg) of the '703 patent is 10,000 times greater than the specifically claimed low does – all falling within the term "effective amount."

[96] "[A] claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed." 35 U.S.C. § 112, ¶ 4.

249. The mean adult male and adult female in the United States weighs 88.8 kg (~195 lb.) and 76.4 kg (~168 lb.), respectively[97]. A dose that ranges from about 0.01 to 100 mg/kg is equivalent to a dose that ranges from about 0.9 mg[98] to 8,900 mg (*i.e.*, 8.9 g) for an adult male and about 0.8 mg to 7,600 mg (*i.e.*, 7.6 g) for an adult female. In other words, as claimed in the '703 patent, the full dose range for a mean adult in the United States is from 0.8 mg to 8.9 g.

250. Accordingly, the dose range (*i.e.*, "effective amount") as described in the specification, and a requirement within each of the asserted claims of the '703 patent, is equivalent to, at a minimum, about an 0.8 mg to 8,900 mg (*i.e.*, 8.9 g) dose for a mean adult in the United States. Thus, the specifically claimed high dose of the '703 patent is about 11,125 times greater than the specifically claimed low dose[99] – all falling within the term "effective amount."[100]

251. Reasonable detail must be provided to a skilled artisan to enable members of the public to understand and carry out the invention. *Genentech*, 108 F.3d at 1366. To supply such details regarding the term "effective amount," Forest and Merz pointed to Example 3 of the '703 patent, which discloses how to make a tablet containing 10 mg of memantine hydrochloride, one of the commercial doses for Namenda. According to Forest and Merz, a person of ordinary skill in the art reading the '703 patent would have been able to orally administer the exemplified 10 mg tablets to a patient diagnosed with Alzheimer's disease without undue experimentation.

252. In further support of this position, Forest and Merz relied upon Experiments E[101] and F[102] of the '703 patent as constituting alleged working examples[103]. In Example E, rats were dosed with memantine at 5 mg/kg and 20 mg/kg. *See* '703 patent, 6:28-50. In Experiment

---

[97] U.S. Dep't for Health & Human Servs., Ctrs. for Disease Control & Prevention, Anthropometric Reference Data for Children and Adults: United States, (2011-2014), at Tables 4 and 6 https://www.cdc.gov/nchs/data/series/sr_03/sr03_039.pdf (last visited June 3, 2017).

[98] 0.01 mg/kg*88.8 kg = 0.888 mg or about 0.9 mg.

[99] 8,900 mg/0.8 mg = 11,125.

[100] Whether the high dose is 10,000 times or 11,125 times greater than the low dose (*i.e.*, depending on how it is calculated) is of little consequence. Either multiple, in my opinion, is very large when considering the full scope of the claimed term "effective amount."

[101] Allegedly to demonstrate that memantine can reduce neuronal damage in the hippocampus caused by carotid artery occlusion.

[102] Allegedly to demonstrate that memantine can protect against NMDA-induced mortality.

[103] In my opinion, these two *in vivo* Experiments are **not** working examples because of a lack of correlation with the claimed method of treatment. *See* Report, Paragraphs 271-274.

F, mice were dosed with memantine at a maximum dose of 50 mg/kg. *See* '703 patent, 6:65-7:6.

253. However, the claimed dosage range in the '703 patent is much broader than the 10 mg, 5 mg/kg, 20 mg/kg, or 50 mg/kg doses of Example 3 and Experiments E and F. The Namenda commercial dose of 10 mg in Example 3 and the 5 mg/kg dose in Experiment E are not near the low end of the broadly claimed dose range of the '703 patent. Moreover, the highest tested dose of 50 mg/kg in Experiment F is not near the high dose of the broadly claimed dose range. In fact, it is one-half of the 100 mg/kg upper dose disclosed in the specification and specifically claimed in the '703 patent.

254. The focus of an enablement inquiry should be whether *everything* within the scope of the claim is reasonably enabled. *AK Steel Corp.*, 344 F.3d at 1244 (providing that "when a range is claimed, there must be reasonable enablement of the scope of the range" and noting that, in that case, that while the claims at issue encompassed amounts of silicon as high as 10% by weight, the specification included statements clearly and strongly warning that a silicon content above 0.5% by weight in an aluminum coating causes coating problems and will not work in the claimed invention); *see also* M.P.E.P. § 2164.08.

255. As related to the Namenda Litigation, I did not find any evidence of record that would show a skilled artisan how to use Namenda at or near its specifically claimed high dose of the 8.9 g or 100 mg/kg. I also did not find any evidence of record to enable a skilled artisan to understand and carry out the specifically claimed method invention at this high dose of 8.9 g or 100 mg/kg.

256. To the contrary, the Namenda Package Insert[104] cautions that "[t]he largest known ingestion of memantine worldwide was *2.0 grams* in a patient who took memantine in conjunction with unspecified antidiabetic medications. The patient experienced *coma*, diplopia and agitation, but subsequently recovered." Namenda Package Insert at 6 (emphasis added).

257. The fact that the Namenda Package Insert warns that the maximum known worldwide overdose of Namenda was 2.0 grams (*i.e.*, about 4.5 times less than the 8.9 g high dose as claimed in the '703 patent), and contributed to a significant adverse event (*e.g.*, coma), in my opinion, indicates that the '703 patent, with its high dose of 8.9 g, claims too broad a dose range to have an enabling disclosure based on the content of the '703 patent specification.

[104] Namenda (memantine HCl) [package insert]. Allergan, plc, 2013. https://www.allergan.com/assets/pdf/namenda_pi (last visited June 16, 2017).

258. When one discloses in the specification and claims a broad dose range of about 0.01 to 100 mg/kg (*i.e.*, 0.8 mg to 8.9 g), one cannot simply ignore any non-enabled or inoperative[105] portion and keep the enabled and operative portion of the claims. *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1368 (Fed. Cir. 2012) (noting that where a patentee claimed a concentration range of 0.0001-5% w/v, but where all concentrations up to 0.001% w/v were not enabled, "then the entire claim is invalid" as "[c]ourts do not rewrite the claims to narrow them for the patentee to cover only the valid portion")[106].

259. Forest and Merz relied on the expert opinion of Rachelle S. Doody, M.D., Ph.D., who stated, in her opposition report that:

> [f]or example, a person weighing 20 kg (~44 lb.) and taking 5 mg/day would be taking 0.25 mg/kg. A patient weighing 200 kg (~440 lb.) taking 20 mg would receive the dose of 0.1 mg/kg. Indeed, I have routinely prescribed Namenda according to manufacturer's instructions as described above, which fall within this range.

Doody Opposition Report at ¶ 35.

260. However, the above-two mg/kg values as calculated by Dr. Doody (0.1mg/kg and 0.25 mg/kg) do not fall near the ends of the broadly claimed dose range of the '703 patent. Doing the math, a "person" taking 5 mg of Namenda based on the 0.01 mg/kg low dose

---

[105] "The utility requirement of 35 U.S.C. § 101 mandates that any patentable invention be useful and, accordingly, the subject matter of the claim must be operable . . . . If a patent claim fails to meet the utility requirement because it is not useful or operative, then it also fails to meet the how-to-use aspect of the enablement requirement" of 35 U.S.C. § 112. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1358 (Fed. Cir.1999) (internal citation omitted); *In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999) (noting that "[i]f the written description fails to illuminate credibility utility, the [US]PTO will make both a section 112, ¶ 1 rejection for failure to teach how to use the invention and a section 101 rejection for lack of utility").

[106] Although *Alcon* was decided by the Federal Circuit in 2012, in my opinion the Federal Circuit's reasoning in *Alcon* does not represent a departure from or change to prior case law on this issue. *See, e.g.*, *AK Steel Corp.*, 344 F.3d at 1244–45 (noting that with respect to enablement, "when a range is claimed, there must be reasonable enablement across the scope of the range" and affirming the district judge's finding of invalidity with respect to enablement); *see also Becton Dickinson & Co. v. C.R. Bard, Inc.*, 922 F.2d 792, 799 n.6 (Fed. Cir. 1990) (noting that "[n]othing in any precedent permits judicial redrafting of claims"); *see also Quantum Corp. v. Rodime, PLC*, 65 F.3d 1577, 1584 (Fed. Cir. 1995) (reasoning that "[a]lthough we construe claims, if possible, so as to sustain their validity, . . . it is well settled that no matter how great the temptations of fairness or policy making, courts do not redraft claims" (citations omitted)). Thus, although at the time of the Namenda Litigation settlements a reasonable and competent patent attorney would not have been able to rely on the *Alcon* decision, per se, a reasonable and competent patent attorney certainly would have been aware of the longstanding propositions which that case supports. *See, e.g.*, *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1349 (Fed. Cir. 2002); *Elekta Instrument S.A. v. O.U.R. Sci. Int'l, Inc.*, 214 F.3d 1302, 1308-09 (Fed. Cir. 2000); *Process Control Corp. v. Hydreclaim Corp.*, 190 F.3d 1350, 1357 (Fed. Cir. 1999); *Rhine v. Casio, Inc.*, 183 F.3d 1342, 1345 (Fed. Cir. 1999).

would weigh 500 kg (~1,100 lb.)[107]. A "person" taking 20 mg of Namenda based on the 0.01 mg/kg low dose would weigh 2000 kg (~4,400 lb.). A "person" taking 5 mg of Namenda based on the 100mg/kg high dose would weigh 0.05 kg (~0.11 lb.). A "person" taking 20 mg of Namenda based on the 100 mg/kg high dose would weigh 0.2 kg (~0.44 lb.).

261. These above calculations emphasize the absurdity of the breath of the dose range as claimed in the '703 patent and confirm the fact that the claimed dose range is too broad to be enabling absent undue experimentation.

262. Granted, a determination whether "undue experimentation" would have been required to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing factual considerations as identified in the seminal case *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) ("**Wands Factors**")[108].

263. According to one practitioner, "[w]hile the courts do not point to any single Wands Factor as dispositive, the case law suggests that the 'level of predictability in the art' factor plays a significant role in virtually all enablement analyses. In addition, any enablement inquiry must necessarily take into account the 'breadth of the claims' since it is the scope of the claims that sets the bounds for any enablement inquiry."[109]

264. Regarding the Wands Factors "Level of Predictability" and "State of the Art," should little be known in the prior art about the nature of the invention, the specification would need more detail as to how to make and use the invention in order to be enabling than otherwise would be required. *See, e.g.*, *Chiron Corp.*, 363 F.3d at 1254; *see also* M.P.E.P. § 2164.03. Similarly, "The Amount of Guidance or Direction" needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970)[110].

265. According to Dr. Joachim Bormann, a named inventor of the '703 patent:

---

[107] 5 mg/(0.01 mg/kg) = 500 kg; 500 kg(2.2 lb./kg) = ~1,100 lb.

[108] The Wands Factors are: "1) the quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or non-predictability of the art, and 8) the breadth of the claims." *Wands*, 858 F.2d at 737.

[109] J. Benjamin Bai, *Enablement Issues Concerning Aggressively Broad Generic Claims*, 7 Nw. J. of Tech. & Intellectual Property, 1, 6 (Fall 2008).

[110] "The 'amount of guidance or direction' refers to that information in the application, as originally filed, that teaches exactly how to make and use the invention." M.P.E.P. § 2164.03.

> [t]he invented concept is that neurodegeneration is caused by calcium overload of the cells and that you can prevent neurodegeneration by memantine or by adamantane derivatives. That's the invention.

Bormann Dep. at 175:4–12.

266. Thus, a named inventor of the '703 patent considered the "Nature of the Invention" of the '703 patent as being the discovery of a *new mechanism of action* hypothesis for memantine and other adamantane derivatives, such as amantadine, involving NMDA receptor channels. At the time of filing the '703 patent, however, Forest and Merz's expert Dr. Malinow acknowledged that little, if anything, was known about this new mechanism of action for administering adamantane derivatives, particularly to treat patients diagnosed with Alzheimer's disease. Malinow Opposition Report at ¶ 43. Dr. Malinow also acknowledged the unpredictability of the state of the art in treating Alzheimer's disease in 1989. *Id.* at ¶ 44.

267. Accordingly, in my opinion, the specification of the '703 patent would need more detail than otherwise provided as to how to make and use the method of treatment invention in order to be enabling. This conclusion is bolstered by the broad breadth of the claimed term of "effective amount" and the state of the art in the 1980s as discussed below.

268. As mentioned above (Report, Paragraph 201), Forest and Merz's Expert, Dr. Malinow cited to no evidence showing that one skilled in the art would understand that the *in vitro* tests were correlated to or indicative of an ability to treat Alzheimer's disease in diagnosed patients. Instead, Dr. Malinow relied on the *unproven hypothesis* presented in the '703 patent that an NMDA antagonist can be used to treat patients with Alzheimer's disease. *See* Malinow Opposition Report at ¶ 52. No additional detail is found in the '703 patent specification.

269. Regarding the Wands Factor "Breadth of a Claim," the relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *AK Steel Corp.*, 344 F.3d at 1244 (reasoning that "there must be reasonable enablement of the scope of the range"); *In re Moore,* 439 F.2d 1232, 1236 (C.C.P.A. 1971) (noting that with respect to enablement, "[t]he relevant inquiry may be summed up as being whether the scope of enablement provided to one of ordinary skill in the art by the disclosure is such as to be commensurate with the scope of protection sought by the claims").

270. As mentioned above (Report, Paragraphs 244, 254), when a broad dose range is claimed as in the present matter, there must be reasonable enablement along the entire scope of the range. As also noted above (Report, Paragraph 255), I, however, did not find any

evidence of record that would show a skilled artisan how to use Namenda at or near its claimed high dose of 8.9 g or 100 mg/kg. I also did not find any evidence of record that would show a skilled artisan how to use Namenda at or near the low dose of 0.01 mg/kg (*i.e.*, 0.9 mg). In my opinion, the scope of enablement that was provided to one skilled in the art by the disclosure in the '703 patent is not commensurate with the breadth of protection sought by the claims.

271. Other Wands Factors involve the presence of absence of "Working Examples" and the "Quality of the Experimentation." Granted, "a specification need not contain a working example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation." *In re Borkowski,* 422 F.2d 904, 908 (C.C.P.A. 1970). A lack of a working example, however, suggests a lack of experimentation quality and thus would be a factor to be considered when exploring "undue experimentation," especially in a case involving an unpredictable and undeveloped art. M.P.E.P. §§ 2164.02, 2164.03.

272. In my opinion, the '703 patent does not contain a working example. An *in vitro* or *in vivo* animal model example in the specification, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention. M.P.E.P. § 2164.02. Based upon my understanding of Dr. Greenberg's Report, *in vivo* Experiments E and F are not correlated to the claimed method of treating patients diagnosed with Alzheimer's disease[111]. Other than providing a hypothesis[112], Dr. Malinow, cited to no evidence showing that one skilled in the art would understand that the *in vitro* tests were correlated to or indicative of an ability to treat Alzheimer's disease in diagnosed patients.

273. Moreover, Dr. Bormann also conceded that the rat experiment in the '703 patent (*i.e.*, "Protection Against Cerebral Ischemia" of test of Experiment E) cannot correlate to

[111] "'Correlation' . . . refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use." *Id.* "If there is no correlation, then the examples do not constitute 'working examples.' In this regard, the issue of 'correlation' is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." M.P.E.P. § 2164.02.

Dr. Greenberg explained that neither experiment was related or correlated to Alzheimer's disease. Rather, the "Protection Against Cerebral Ischemia" test of Experiment E was recognized as relating to "transient forebrain ischemia (brain damage following cardiac arrest)," and that the "Protection Against NMDA-Induced Mortality" test of Experiment F was recognized as relating to "NMDA overdose." Greenberg Report at ¶ 16. *See* Report, Paragraphs 204-205.

In response, Dr. Malinow took the position that the Experiments E and F enabled one skilled in the art to use memantine to treat Alzheimer's disease because the "pathological activation of NMDA receptors" was "*thought* to occur in Alzheimer's disease." Malinow Opposition Report at ¶ 36. However, Dr. Malinow did not offer any evidence showing that one skilled in the art would have such understanding at the relevant time. *Id.*

[112] In effect, that "pathological activation of NMDA receptors" was "*thought* to occur in Alzheimer's disease." Malinow Opposition Report at ¶ 36.

humans. He testified that "[y]ou cannot compare doses in the rat with doses that have the same effect in humans." Bormann Dep. at 228:1–3.

274. Accordingly, in my opinion, a lack of a working example in an unpredictable art is indicative of a lack of enablement commensurate with the scope of the claimed dose range of the '703 patent.

275. Even assuming that Experiments E and F were considered working examples for the purposes described therein, in my opinion, those examples fail to teach those skilled in the art how to use the claimed invention along the entire claimed dose range – *i.e.*, at the low and high ends of the claimed dose range. *See* Report, Paragraph 253. In other words, the amount of memantine used in these experiments is much lower than the claimed high dose and much higher than the claimed low dose.

276. The courts, however, have recognized that "a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands,* 858 F.2d at 737.

277. "In the chemical arts, the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed." M.P.E.P § 2164.06.

278. The disclosure in the '703 patent specification would not teach a skilled artisan what routine testing could be conducted to enable a skilled artisan to use the claimed invention over its entire scope. For example, the lack of a working example, the breadth of the specifically claimed dose range, and the unpredictability of the art would leave a skilled artisan with little guidance to determine what tests to conduct to determine how to use the claimed method of treatment over the entire length of the claimed dose range.

279. Moreover, *In re Gardner*, 427 F.2d 786 (C.C.P.A. 1970), a seminal case in the area of the enablement requirements for method of treatment claims, is instructive. It supports the position that the dose range claimed in the '703 patent is too broad to be enabled by its specification.

280. In *In re Gardner*, the invention concerned a discovery of the antidepressant activity of certain pharmaceutical compounds. 427 F.2d at 786. The invention resided in using certain compounds to alleviate depression. *Id.* One method claim called for administering an "effective amount" of the pharmaceutical compound. *Id.* at 788. Two other method claims called for administering "daily doses" in the ranges from about 10 to 450 mg (*i.e.*, a range of 1 to 45 times) or 10 to 300 mg[113]. *Id.* Example 18 of the Gardner patent

[113]According to the *Gardner* court, "[t]hey are enormously wide ranges," 427 F.2d at 788, and "[w]ith that range, the use of "about" seems somewhat superfluous." *Id.*

"showed four specific dosage unit forms [and] capsules containing 10, 25, 50, and 100 mg of active ingredient." *Id.* The specification lacked working examples.

281. The method claims were rejected as being based on a defective specification that failed to teach one skilled in the art how to use the invention as required by 35 U.S.C. §112 (*i.e.*, enablement). *Id.* at 789.

282. The court rejected Gardner's argument that a skilled artisan could figure out how to use the invention. According to Judge Rich:

> [Gardner argues that] those skilled in the art, by investigations along the above lines [using known antidepressant drug as standards], and by a great amount of work, can eventually find out how to use [Gardner's] invention. But our view is that the law requires that the disclosure in the application shall inform them how to use, not how to find out how to use for themselves. The above argument is self-defeating. It demonstrates the inadequacy of the disclosure by saying, in effect: We have detected and disclosed the presence of activity; if you wish to practice our invention, go and find out how to use it.

Id. at 789. As a result, the court affirmed the rejection of Gardner's method of treatment claims as not being enabled under 35 U.S.C. §112. *Id.*

283. Analogous to the *Gardner* case, the '703 invention concerns an alleged discovery of pharmaceutical activity of adamantane derivatives. This method of treatment invention allegedly resided in the discovery of a new mechanism of action of adamantane derivatives on NMDA receptor channels for the treatment of Alzheimer's disease. All of the '703 patent method claims called for administering "an effective amount" of these compounds in a dose that, in effect, ranged from about 0.8 mg to 8.9 g (*i.e.*, a range of 1 to 11,125 times[114]). Example 3 of the '703 patent shows how to make capsules containing 10 mg of active ingredient. However, the specification lacks working examples.

284. As in *Gardner*, in my opinion, the inventors of the '703 patent also were saying, we have detected and disclosed the presence of activity through as new mechanism of action to treat Alzheimer's patients. If you wish to practice our invention within its broad dose range, go and find out how to use it.

285. An attempt to gain protection for a "'mere germ of an idea does not constitute enabling disclosure.'" *In re '381 Patent Infringement Litigation*, 583 F.3d at 1323–24 (quoting *Genentech*, 108 F.3d at 1366).

[114] *See also* Report, Footnote 100.

286. As in *Gardner* and in my opinion, the '703 method of treatment claims are invalid because they are not enabled by the specification under 35 U.S.C. § 112, ¶ 1.

287. Based upon my review, there is nothing in the record that teaches those skilled in the art how to use the full scope of the claimed dose range, without undue experimentation.

288. In my opinion, the '703 patent was not enabled because of the broad breadth of the claim term "effective amount."

(4) Conclusion

289. In my opinion, a reasonable and competent patent attorney would have realized that Mylan would have met its burden and would be more likely than not to prevail with regard to invalidating the claims of the '703 patent as not being enabled under 35 U.S.C. § 112, ¶ 1 based the breadth of the claimed term "effective amount." Simply put, the claimed term "effective amount" is not enabled over its full scope.

290. Taking all of the above into consideration, in my opinion, a reasonable and competent patent attorney would have realized that the chance of success was about 60% in favor of Mylan to about 40% in favor of Forest and Merz for Mylan to invalidate the claims of the '703 patent for lack of enablement under 35 U.S.C. § 112 based on the "effective amount" argument.

4. 35 U.S.C. § 156 – Patent Term Extension

291. To invalidate the patent term extension of the '703 patent, Mylan had the burden to demonstrate under the clear and convincing standard that Forest and Merz did not comply with the requirements under 35 U.S.C. § 156 when procuring the patent term extension for the '703 patent. *Pfizer Inc. v. Ranbaxy Labs., Ltd.*, 405 F. Supp. 2d 495, 511–12 (D. Del. 2005), *aff'd in part, rev'd in part on other grounds*, 457 F.3d 1284 (Fed. Cir. 2006).

a. Mylan's Position

292. Mylan's position in the Namenda Litigation was that all or a portion of the 5-year patent term extension of the '703 patent was invalid due to the material failure of patent owner (Merz) and its agent (Forest) to provide correct information (*e.g.*, for due diligence) as required by 35 U.S.C. § 156. Mylan contended that Forest and Merz's material failure was the result of bad faith, gross negligence, or reckless indifference to whether their representations to the USPTO and HHS Secretary were true or false. *See, e.g.*, Pretrial Order, Exhibit 12, ¶¶ 199–234.

b. Forest and Merz's Position

293. Forest and Merz' position in the Namenda Litigation was that, first, under 35 U.S.C. § 282 the issue of due diligence during the regulatory review period is irrelevant outside the context of a timely filed due diligence petition under 35 U.S.C. § 156(d)(2)(B) (**"due diligence petition"**). Second, Forest and Merz argued that they had complied with all the requirements of 35 U.S.C. § 156. Third, Forest and Merz asserted that Mylan never pleaded that the '703 patent or its patent term extension are unenforceable due to any alleged inequitable conduct. Forest and Merz also asserted that Mylan failed to plead with particularity any facts necessary to establish that Forest and Merz engaged in inequitable conduct with respect to the '703 patent. *See, e.g.*, Pretrial Order, Exhibit 11, ¶¶ 241–80, 394–95.

c. Analysis[115]

294. Before discussing Forest and Merz's 35 U.S.C. § 156 compliance failures as alleged by Mylan, for the sake of procedural order, I first shall consider Forest and Merz's alleged position under 35 U.S.C. § 282.

(1) Due Diligence Review outside of a Due Diligence Petition – 35 U.S.C. § 282(a)

295. Under 35 U.S.C. § 282(c), in any action involving infringement of a patent during the period of the extension of its term, "[a] due diligence determination under section 156(d)(2) is not subject to review in such an action."

296. In my opinion, a reasonable and competent patent attorney at the time of the Namenda Litigation settlement would have realized that it would be more likely than not for Forest and Merz to prevail on the 35 U.S.C. § 282 issue. In other words, it would be likely for the District Court to hold that due diligence determinations cannot be challenged in a patent litigation outside of a due diligence petition.

297. To support their position:

- First, Forest and Merz interpreted the language of 35 U.S.C. § 156(d)(2)(B)(i), to mean that whether a PTE Applicant acted with due diligence during the applicable regulatory review period is subject to a determination by the FDA ***only*** upon the

[115] For a more detailed discussion of the applicable law, see Exhibit M.

petition of a third party within 180 days of the publication of that regulatory review period in the Federal Register ("due diligence petition")[116, 117].

- Second, Forest and Merz also interpreted the language of 35 U.S.C. § 156(c)(1) to mean that the number of days during which a PTE Applicant "did not act with due diligence" is subtracted from the regulatory review period ***only*** when the FDA makes such a determination upon a timely third-party due diligence petition (*i.e.*, a petition submitted no later than 180 days after the regulatory review period is published in the Federal Register)[118].

- Third, Forest and Merz relied on the last sentence of 35 U.S.C. § 282(a), which states that "[a] due diligence determination under section 156(d)(2) is not subject to review" in a patent infringement action[119].

298. In my opinion, the language of 35 U.S.C. § 282(c) and that of the other statutory references noted above support Forest and Merz's position that due diligence determinations cannot be challenged in a patent litigation involving a patent term extension outside of a due diligence petition[120]. This conclusion, however, does not end my analysis.

299. Instead, Mylan was arguing that it was not challenging the *due diligence determinations* in the Namenda Litigation. In particular, it was challenging neither the *specific dates and specific duration* of the testing and approval phases as determined by the HHS Secretary nor the resulting USPTO's *calculation* regarding the exact days of the patent extension.

300. Instead, Mylan was asserting a separate and different issue. Mylan was challenging whether Forest and Merz submitted to the USPTO and the HHS Secretary all the information that is required to be provided under 35 U.S.C. § 156. In other words, Mylan was asserting its separate right to have a court review Forest and Merz's compliance with

[116] For completeness, I note that 35 U.S.C. § 156(d)(2)(B)(ii) states that "[a]***ny interested person*** may request . . . the Secretary making the determination to hold an informal hearing on the determination." (emphasis added). In my opinion, filing the request is not restricted to third parties.

[117] Pretrial Order, Exhibit 11, ¶ 260.

[118] Pretrial Order, Exhibit 11, ¶ 261.

[119] Pretrial Order, Exhibit 11 ¶ 262.

[120] As the HHS Secretary noted in a February 21, 2008 letter to the USPTO, FDA did not receive any due diligence petitions regarding Namenda in which "any interested person could file a petition with FDA under 35 U.S.C. § 156(d)(2)(B)(i) for a determination of whether the patent term extension applicant acted with due diligence during the regulatory review period." As a result, "FDA considere[d] the regulatory review period determination to be final."

the requirements of 35 U.S.C. § 156, independent of any restrictions on due diligence determinations as imposed under the above sentence of 35 U.S.C. § 282(c).

301. In my opinion, the legislative history of what ultimately became 35 U.S.C. § 156 supports Mylan's position that it was asserting a separate and different issue involving compliance under 35 U.S.C. § 156. These compliance requirements, *inter alia*, include the PTE Applicant's obligation to act with candor and good faith (*i.e.*, duty of disclosure obligations) under 35 U.S.C. § 156(d)(4) and its regulations 37 C.F.R. §§ 1.740, 1.765, and the PTE Applicant's obligation to provide material information to enable the USPTO to determine the eligibility of a patent for extension under 35 U.S.C. § 156(d)(1)(C) and its regulations 37 C.F.R. §§1.740, 1.775.

302. The applicable House Report provides:

> [t]o obtain an extension, the patent owner or its agent would submit an application to the Commissioner of Patents and Trademarks within 60 days of approval of the approved product. The application would contain the information described in subparagraphs (A)-(G) of section 156(d)(1). *The applicant would be subject to any disclosure requirements prescribed by the Commissioner. The Committee expects that those requirements would subject the applicant to at least the same duty of disclosure, and the penalties and loss of rights for violation of the duty of disclosure, which governs all patent application proceedings before the Patents and Trademarks Office.*

H.R. Rep. No. 98-857, pt. 1, at 41 (1984) (emphasis added); *see also* 130 Cong. Rec. H8707-H8709 (daily ed. Aug. 8, 1984) (statement of Rep. Kastenmeier).

303. Based on my reading of the above legislative history, Congress intended a PTE Applicant to be subject to at least the same duty of disclosure obligation which governs all patent applicant proceedings.

304. Accordingly, in my opinion, a reasonable and competent patent attorney at the time of the Namenda Litigation settlement would have recognized that the District Court's analysis would *not* have ended with its merely interpreting the statutory language prohibition of 35 U.S.C. § 282(c). The court would have wanted to hear Mylan's noncompliance arguments under 35 U.S.C. § 156 against Forest and Merz.

(2) PTE Applicant's Alleged Failure to Comply with 35 U.S.C. § 156(d)(1)(C) (Information to Determine the Period of Extension)

305. Under 35 U.S.C. § 282(c):

> [i]nvalidity of the extension of a patent term or any portion thereof under . . . section 156 because of the *material failure ...by the applicant for the [patent term] extension . . . to comply with the requirements of such section shall be a defense in any action involving the infringement of a patent* during the period of the extension of its term and shall be pleaded.

(emphasis added).

306. In turn, 35 U.S.C. §156(d)(1)(C) requires that a PTE Application contain:

> information to enable the [USPTO] Director to determine . . . the eligibility of a patent for extension and the rights that will be derived from the extension and information to enable the [USPTO] Director and the Secretary of Health and Human Services . . . to determine the period of the extension under subsection (g) . . . .

307. In my opinion, Mylan met its burden of demonstrating that the PTE Applicant failed to comply with the requirement under 35 U.S.C. § 156(d)(1)(C) and its regulations (37 C.F.R. §§ 1.740, 1.775).

308. In the PTE Application, Forest and Merz stated that the effective date of the IND for Namenda was October 9, 1997, the date on which the FDA "reactivated" the IND after it previously was "inactivated" by Merz. Because Forest and Merz were not relying on activities occurring before October 9, 1997, any due diligence (or number of days lacking due diligence) occurring prior to October 1997 was not relevant to the determination of patent term extension under 35 U.S.C. § 156.

309. In the PTE Application, Forest and Merz also provided, under 37 C.F.R. § 1.775(d)(1)(ii), the number of days within the testing and approval phases of the regulatory review period during which Forest and Merz failed to act with due diligence[121]. The number of days provided was zero.

[121] For purposes of this section, the term "**due diligence**" means "that degree of attention, *continuous directed effort,* and timeliness as may reasonably be expected from, and are ordinarily exercised by, a person during a regulatory review period." 35 U.S.C. § 156(d)(3) (emphasis added).

310. Later during prosecution of the PTE Application, the HHS Secretary corrected the effective date of the IND for Namenda from the date Forest and Merz provided in the PTE Application. According to FDA's records[122], the IND for Namenda had an effective date of February 7, 1990, rather than October 9, 1997 identified by Forest and Merz. Thus, the HHS Secretary *expanded* the testing phase to include the time between February 7, 1990 and October 9, 1997.

311. In my opinion, once the HHS Secretary corrected the effective date of the IND to be February 7, 1990, Forest and Merz's due diligence activities during the resulting *expanded* time period became relevant. But, Forest and Merz never updated the USPTO and the HHS Secretary on due diligence during the expanded testing phase.

312. While the term "material failure" is not specifically defined in 35 U.S.C. § 282(c), in my opinion, Forest and Merz's failure to bring the above information on due diligence to the attention of the USPTO and to the HHS Secretary while the PTE Application was pending constituted a *material* failure to comply with the requirements of 35 U.S.C. § 156(d)(1)(C)[123]. This information, known by Forest and Merz, could have significantly affected the number of days that the USPTO granted for the patent term extension of the '703 patent. Each additional day of patent term extension was significant to Forest and Merz[124].

313. As a result and in my opinion, Forest and Merz, through their representatives, were obligated[125] to amend or supplement the PTE Application or file a due diligence petition

---

[122] The FDA considers the testing phase to have begun when the *first* IND for the approved drug product became effective. *See, e.g.*, FDA, Determination of Regulatory Review Period for Purposes of Patent Extension, MIFEPREX; Amendment, 67 Fed. Reg. 65358, 65358–59 (Oct. 24, 2002), *available at* https://www.gpo.gov/fdsys/pkg/FR-2002-10-24/pdf/02-27096.pdf (last visited July 8, 2017) (concluding that the testing phase for Mifeprex began with the first IND filed in 1983 for mifepristone alone and not the second IND filed in 1994 for mifepristone followed administration of misoprostol, which was ultimately the subject of the approved NDA).

[123] My opinion regarding what is a "material failure" under 35 U.S.C. § 156(d)(1)(C) is consistent with the meaning of the term "material" as used regarding section of 35 U.S.C. § 156(d)(4) and its regulation 37 C.F.R. § 1.765(a). Under this regulation, information is material where there is "a substantial likelihood" that the USPTO or HHS Secretary "would consider it important in determinations to be made in the patent term extension proceeding." 37 C.F.R. § 1.765(a).

[124] According for Forest and Merz, gross sales of Namenda in Fiscal Year 2009 exceeded $1 billion. Pretrial Order, Exhibit 11, ¶ 13. This translates to average Namenda daily sales of over $2.7 million ($1,000,000,000/365 = ~$274,000,000). Assuming sales remained constant, for every day that the patent was extended, Forest and Merz received over $2,700,000. In my opinion, with this amount of money at stake every day, Forest and Merz knew or should have known that the gaps in information on due diligence were material and, thus, should have been disclosed to the USPTO and the HHS Secretary.

[125] A practitioner having business before the USPTO is bound by the USPTO Code of Professional Responsibility. *See* 35 U.S.C. §§ 2(b)(2)(D) 32; 37 C.F.R. §§ 11.5(b), 11.19. With the signing of a paper filed in any proceeding before the USPTO, there comes an implied certification that "[t]he allegations and other factual contentions

to update the USPTO and HHS Secretary with regard to their due diligence activities during the *expanded* testing phase, including the number of days (if any) within the *expanded* testing phase during which there was a lack of due diligence, if any.

314. In response, Forest and Merz would have asserted at trial that because they provided in the PTE Application information regarding due diligence (*e.g.*, starting July 10, 1998), there was no need under 35 U.S.C. § 156(d)(1)(C) for Forest and Merz to inform the USPTO or the HHS Secretary about anything further.

315. In particular, Forest and Merz would have directed the District Court's attention to the Chronology of Regulatory Review of Namenda to the '703 patent that was part of their PTE Application, as originally filed[126]. This Chronology included certain activities during part of the expanded testing phase. For example, Forest and Merz referenced the initial IND submission (7/10/89), Annual Report (4/29/91), identified G.H. Besselaar Associates as their new US Agent (1/23/92), submitted a Protocol Amendment (7/31/92), provided a Response to FDA Request for Information (8/13/92), provided a Response to Clinical Hold - Revised Investigator's Brochure (1/20/93), submitted an IND Annual Report (9/13/93), provided a Request for Inactivation of IND (1/13/94), and provided a Request for Reactivation of the IND (8/29/97).

316. But, there were no entries in the Chronology from January 13, 1994 through August 29, 1997[127], during the remainder of the expanded testing phase. The PTE Application was never updated. Thus, the Chronology entries do not cover the entire *expanded* testing phase. Even *assuming* that the activities noted in the Chronology were sufficient for due diligence purposes during a portion of the Chronology's above time period, these entries did not cover "gaps" in due diligence during the *expanded* testing phase[128].

317. Moreover, and in my opinion, Merz appeared to admit that there was a lack of due diligence activities at least from September 13, 1993 through January 1994. In a letter to

---

[asserted in the paper] have evidentiary support for or, if specifically so identified, are likely to have evidentiary support after a reasonable opportunity for further investigation or discovery." 37 C.F.R. § 11.18(b)(2)(iii). Should the person later find that that the allegations or representations made in a paper were not accurate or did not have evidentiary support after a reasonable inquiry, it is incumbent on the person to file a subsequent paper in the USPTO to correct any allegation or other factual contention that is not supported. Failure to comply with 37 C.F.R. § 11.18 may subject a practitioner to discipline by the USPTO. *See* 37 C.F.R. § 10.23(c)(15) (providing that misconduct before the USPTO includes "[s]igning a paper filed in the [USPTO] in violation of the provisions of § 11.18 or making a scandalous or indecent statement in a paper filed in the [USPTO]").

[126] *See* Exhibit J of the Patent Term Extension Application for the '703 patent.

[127] On October 9, 1997, the FDA reactivated the IND.

[128] Due diligence requires "continuous directed effort." *See* 35 U.S.C. § 156(d)(3).

the FDA dated January 13, 1994, Dr. Gregory M. Hockel, Ph.D., Senior Director, Regulatory Affairs, G.H. Besselaar Associates (acting as agent for Merz) stated:

> The last Annual Report for memantine under this IND was submitted on 13 September 1993 as Serial No. 011. As indicated in that report no clinical studies were undertaken in the annual reporting period. No clinical studies have occurred since that submission and no clinical studies are planned in the near future.

FRX-AT-02191000.

318. Accordingly, there was no indication in the PTE Application (including the Chronology) of any due diligence activities occurring after September 13, 1993 through reactivation of the IND.

319. For completeness, a timeline regarding the alleged due diligence activities for Namenda as found in the PTE Application is presented as attached Exhibit N. In this Exhibit, I provided a timeline of events and days during the expanded testing phase of the regulatory review period. For example, based on the Chronology, I noted: a) the entries (and the number of days) where Forest and Merz apparently alleged due diligence activities, b) the time period (and number of days) where there is no indication in the PTE Application of Forest and Merz's due diligence, and c) the date the '703 patent issued[129].

320. In response, Forest and Merz also would have directed the District Court's attention to their alleged due diligence activities outside the United States where Merz was pursuing clinical research of memantine in patients with dementia of the Alzheimer type[130]. In particular, Forest and Merz would have directed attention to two clinical studies on Namenda that were conducted during the *expanded* testing phase - the first, between October 12, 1992 and July 18, 1994, Study No. MRZ 90001-9104 at four centers in France; and the second, between November 1994 and July 1995, Study No. MRZ 90001-9403, at seven centers in Latvia.

321. Granted, these two above studies might have filled in some of the time periods (*i.e.*, "gaps") regarding due diligence that were not covered by the Chronology. But, these studies were never brought to the attention of the USPTO or the HHS Secretary during the pendency of the PTE Application of the '703 patent. They were never submitted as a supplement to the PTE Application or as part of a due diligence petition, to be considered

[129] The patent issuance was included because the time during the regulatory review period that occurred before the patent issuance is subtracted from the USPTO's patent term extension calculation.

[130] Based upon my review of the record, these studies were identified for the first time in Pretrial Order, Exhibit 11, ¶¶ 272 –76. They were, however, never a part of the PTE Application.

by the HHS Secretary and the USPTO. In my opinion, after the PTE Application was concluded and the Certificate of Patent Extension issued, it was too late for Forest and Merz to have these studies considered for due diligence purposes.

322. In my opinion, Forest and Merz failed to provide in their PTE Application material information on due diligence regarding the expanded testing phase to the HHS Secretary and the USPTO. As a result, Forest and Merz failed to fill in the above "gaps" regarding the number days within the *expanded* testing phase during which there was a lack of due diligence, if any. Thus, Forest and Merz failed to comply with their obligations under 35 U.S.C § 156(d)(1)(C) and its regulation 37 C.F.R. § 1.775.

323. As a result and in my opinion, the number of days that the USPTO granted for the patent term extension of the '703 patent on account of the expanded testing phase should have been eliminated from the patent term extension. As a minimum, a court would have reduced the number of days that the '703 patent was extended in its Certificate of Patent Term Extension to the amount of time Forest and Merz requested in their original Patent Term Extension Application. In other words, the Certificate, at a minimum, would have been revised to extend the term of the '703 patent by only 1,250 days (approximately 3.4 years, *i.e.*, with an extension expiring on September 12, 2013), rather than by 5 years (*i.e.*, with an extension expiring on April 11, 2015). Should a court so modify the Certificate, Forest and Merz would not have benefited from their failure to update the USPTO and the HHS Secretary with material information in violation of 35 U.S.C § 156(d)(1)(C).

324. As a result and in my opinion, a reasonable and competent patent attorney at the time of the Namenda Litigation settlement would have realized that Mylan could have met its burden and could have invalidated at least a portion of (or the entire) the Certificate of Patent Term Extension of the '703 patent (*i.e.*, at least beyond Forest and Merz's originally requested 1,250 days extension) because of Forest and Merz's material failure to comply with the obligations of 35 U.S.C § 156.

(3) PTE Applicant's Alleged Failure to Comply with 35 U.S.C. § 156(d)(4) (Duty of Disclosure)

325. Under 35 U.S.C. § 156(e)(1), a determination that a patent is eligible for extension "may be made by the [USPTO] Director solely on the basis of the representations contained in the application for the extension." Thus, the USPTO and the HHS Secretary may rely on a PTE Applicant's representations in a request for extension of patent term for purposes of making a determination of how much the term of the patent should be extended.

326. To help ensure that a PTE Applicant's representations are reliable, 35 U.S.C. § 156(d)(4) states that "[a]n application for the extension of the term of a patent is subject to the

disclosure requirements prescribed by the Director [of the USPTO]." These disclosure requirements established a "duty of candor and good faith" ("**duty of disclosure**") toward the USPTO and the HHS Secretary during the prosecution of a PTE Application. 37 C.F.R. §§ 1.740, 1.765. The duty applies to the patent owner and its agent[131] (*i.e.*, Forest and Merz).

327. According to 37 C.F.R. § 1.765(a), a PTE Applicant must disclose to the USPTO or the HHS Secretary "material information adverse to a determination of entitlement to the extension sought." Information is "material" where there is a substantial likelihood that the USPTO or HHS Secretary "would consider it important in determinations to be made in the patent term extension proceeding." *Id.* Such material information must be brought to the attention of the USPTO or the HHS Secretary "as soon as it is practical to do so after the individual becomes aware of the information." *Id.*

328. Once HHS expanded the testing phase to include the time period from February 7, 1990 to October 9, 1997, Forest and Merz's due diligence activities during such expanded time period became *material* under 37 C.F.R. § 1.765(a)[132]. In my opinion, there is a substantial likelihood that the USPTO and HHS Secretary would have considered such information important to a determination of entitlement to the extension sought for the patent term extension proceeding of the '703 patent[133]. This information, which was either known or should have been known by Forest and Merz, could have significantly affected the number of days that the USPTO granted for the patent term extension of the '703 patent, and each additional day of patent term extension was significant to Forest and Merz. In my opinion, Forest and Merz knew or should have known of the materiality of this missing information.

329. In response, Forest and Merz at trial would have asserted that they identified, in the PTE Application, their due diligence activities as required by 35 U.S.C. § 156 (Report, Paragraph 314). As discussed above (Report, Paragraph 315), they would have directed attention to the Chronology of Regulatory Review of Namenda to the '703 patent[134] and to two previously mentioned clinical studies on Namenda that were conducted during the

[131] The duty also applies to each attorney or agent who represents the patent owner and on every other individual who is substantively involved on behalf of the patent owner in a patent term extension proceeding. 37 C.F.R § 1.765(a).

[132] For efficiency, I shall attempt to avoid repeating some of the factual details that were presented in prior subsection (2), but I incorporate by reference the content of that subsection into this subsection (3).

[133] A determination that a patent is eligible for extension may be made by the Director of the USPTO solely on the basis of the representations contained in the application for the extension. 35 U.S.C. § 156(e)(1).

[134] See Exhibit J of the Patent Term Extension Application for the '703 patent.

expanded testing[135]. But, there were no entries in the Chronology after January 13, 1994 through August 29, 1997[136], during the remainder of the expanded testing phase. The PTE Application was never updated. Thus, the Chronology entries do not cover the entire expanded testing phase. Moreover, and as previously explained (Report, Paragraph 317), there was no indication in the PTE Application (including the Chronology) of any due diligence activities occurring after September 13, 1993.

330. And, these two studies were neither included in the Chronology nor elsewhere in the PTE Application. Simply put, there were times during the e*xpanded* testing phase when Forest and Merz did not provide in the PTE Application or update any information in the PTE Application on due diligence (or a lack of due diligence). *See, e.g.*, attached Exhibit N. For the reasons previously mentioned and in my opinion, this information would have been material to the USPTO and HHS Secretary's determinations of entitlement to the extension sought for the patent term extension proceeding of the '703 patent.

331. In my opinion, by knowingly remaining silent rather than updating the USPTO and HHS Secretary regarding due diligence during the entire expanded testing phase, Forest and Merz violated their duty of disclosure obligations of 35 U.S.C. § 156(d)(1)(C) and its regulations (37 C.F.R. §§ 1.740, 1.765) through bad faith or gross negligence[137].

332. Failure to provide material information has consequences[138] under the standard promulgated by 37 C.F.R. § 1.765(c):

> [i]f it is established by clear and convincing evidence that . . . there was any *violation of the duty of disclosure through bad faith or gross negligence* in connection with the patent term extension proceeding, a final determination will be made that the *patent is not eligible for extension.*

(emphasis added).

---

[135] Pretrial Order, Exhibit 11, ¶¶ 270, 272–77.

[136] On October 9, 1997, the FDA reactivated the IND.

[137] The terms "bad faith" and "gross negligence" are not defined in the regulations. However, the terms have common meanings. "Bad faith" is defined as "[d]ishonesty of belief or purpose." *Bad faith*, BLACK'S LAW DICTIONARY, (9th ed. 2009). "Gross negligence" is defined as "[a] lack of slight diligence or care" or [a] conscious, voluntary act or omission in reckless disregard of a legal duty and of the consequences to another party, who may typically recover exemplary damages." *Gross negligence,* BLACK'S LAW DICTIONARY, (9th ed. 2009).

[138] As noted above (Report, Section XI.B.4.c.2), invalidity of a patent term extension shall be a defense in an infringement action because of the PTE Applicant's material failure to comply with the requirements of 35 U.S.C. § 156. 35 U.S.C. § 282(c).

333. Rather than bringing the gaps on due diligence to the attention of the USPTO and the HHS Secretary, Forest and Merz knowingly (or should have known that they) filed a statement with the USPTO that affirmatively sought to expedite the USPTO's final issuance of the patent term extension for the '703 patent.

334. Specifically, in response to the USPTO's notification of its calculation of the patent term extension, Forest and Merz filed a "Waiver of Reconsideration of Notice of Final Determination," in effect, accepting the USPTO's PTE calculation. In this filing, Merz's newly empowered patent attorney[139], on behalf of Merz, stated that it "respectfully accepts this determination with appreciation" and further requested that the USPTO issue the extension "at the earliest possible time."

335. In my opinion, when they received the USPTO's above notification, Forest and Merz knew or should have known that they had requested only 1,250 days in the PTE application, while the USPTO's notification provided for 2,336 days without subtracting any days for lack of due diligence. Because of Forest and Merz's failure to fill in the gaps regarding its due diligence (or lack of due diligence) during the *expanded* testing phase, the USPTO relied on the PTE Applicant's originally submitted information and did not subtract any days for a lack of due diligence.

336. In my opinion, Merz's new patent counsel filed the "Waiver of Reconsideration" even though Forest and Merz knew or should have known that the determinations by the HHS Secretary and the USPTO were based on the PTE Applicant's prior submission of information to the USPTO in the PTE Application. Forest and Merz knew or should have known that there were gaps in the due diligence information the USPTO and the HHS Secretary relied upon in making their determinations in the patent term extension proceeding for the '703 patent. They knew or should have known that their prior

[139] After Merz became aware that the HHS Secretary expanded the testing phase, Merz revoked the power of attorney of the law firm that was *substantially involved* with and should have been knowledgeable (or should have inquired) about due diligence (or lack thereof) during the *expanded* testing phase for Namenda. Instead, Merz transferred the power of attorney to another law firm. I do find curious the timing of Merz's change of attorneys in light of the PTE Applicant's apparent knowledge that the USPTO's patent term extension calculations did not account for the number of days that the PTE Applicant may have failed to act with due diligence during the entire *expanded* testing phase.

Even assuming that when the power of attorney to the prior firm involved in the PTE Application was revoked and the attorneys at the prior firm who were substantially involved with the prosecution of the PTE Application were no longer authorized to communicate on behalf of the PTE Applicant with the USPTO or the HHS Secretary, Forest and Merz retained their duty of disclosure obligation to disclose material information on due diligence of which they were aware.

Even assuming the new firm had no knowledge regarding the failure to provide material information on due diligence under 35 U.S.C. § 156(d)(4), the PTE Applicant retained its duty of disclosure obligation to disclose material information on due diligence of which it was aware.

submissions in the PTE Application did not take into consideration due diligence during the full duration of the expanded testing phase.

337. In sum and in my opinion, Forest and Merz:

- knew or should have known that the USPTO in its determination credited Forest and Merz for being diligent during the full duration of the expanded testing period because the USPTO relied on the representations on due diligence made in the original PTE Application;

- knew or should have known that the missing information on due diligence during the full expanded testing phase was material to the USPTO's patent term extension calculation for the '703 patent;

- failed to update the USPTO and the HHS Secretary with the missing material information on due diligence; and

- affirmatively accepted a 5-year patent term extension (*i.e.*, through April 11, 2015) based on the USPTO's patent term extension calculation for the '703 patent.

338. As a result and in my opinion, Forest and Merz, violated their duty of disclosure obligations under 35 U.S.C § 156(d)(4) and its regulations 37 C.F.R. §§ 1.740, 1.765 by exhibiting bad faith or gross negligence in connection with their dealings with the USPTO and the HHS Secretary during the patent term extension proceeding.

339. In my opinion, a reasonable and competent patent attorney at the time of the Namenda settlement would have recognized that:

- Mylan could have met its burden and could prevail in proving that Forest and Merz knowing failed to update the USPTO and the HHS Secretary with material information on due diligence during the fully expanded testing phase; and

- Forest and Merz's actions constituted a bad faith or gross negligence violation of its duty of disclosure obligations under 35 U.S.C § 156(d)(4) as well as the standard established under 37 C.F.R. § 1.765.

340. As a result, the '703 patent was not eligible for a patent term extension.

341. Moreover, in my opinion, because Forest and Merz violated their duty of disclosure obligations under 35 U.S.C § 156(d)(4) and 37 C.F.R. § 1.765, a reasonable and competent patent attorney would have recognized that the *entire* patent term extension of the '703 patent should not have been granted and the *entire* extension would have been

invalidated by the district court. In my opinion, the consequence of violating a duty of disclosure obligation under 37 C.F.R. § 1.765 during prosecution of patent term extension application would be analogous to the consequence of violating a duty of disclosure under 37 C.F.R. § 1.56 during prosecution of a patent application. That is, "no patent will be granted on an application in connection with which . . . the duty of disclosure was violated through bad faith or intentional misconduct." 37 C.F.R. § 1.56(a).

342. As noted above (Report, Paragraph 302), Congress intended a PTE Applicant to be subject to *at least* the same consequence for a duty of disclosure violation under 35 U.S.C § 156 (37 C.F.R. § 1.765) for prosecuting a patent term extension application as govern prosecuting a patent application under 37 C.F.R. § 1.56.

343. According to the applicable House Report regarding what became 35 U.S.C § 156:

> The [patent term extension] applicant would be subject to any disclosure requirements prescribed by the Commissioner. The Committee expects that those requirements would subject the applicant to *at least the same duty of disclosure, and the* ***penalties and loss of rights for violation of the duty of disclosure****, which governs all patent application proceedings before the Patents and Trademarks Office.*

H.R. Rep. No. 98-857, pt. 1, at 41 (1984) (emphasis added); *see also* 130 Cong. Rec. H8707-H8709 (daily ed. Aug. 8, 1984) (statement of Rep. Kastenmeier).

344. As a result and in my opinion, a reasonable and competent patent attorney at the time of the Namenda settlement would have realized that Mylan could have met its burden and could have invalidated the *entire* Certificate of Patent Term Extension of the '703 patent for failure to comply with 35 U.S.C § 156, thus returning the term of the patent to its original expiration date of April 11, 2010.

(4) Asserting Defenses – 35 U.S.C § 156 Disclosure Obligations vs. Inequitable Conduct

345. Forest and Merz asserted that Mylan never pleaded that the '703 patent or its patent term extension are unenforceable due to alleged inequitable conduct[140]. Therefore, they argued, the court should not consider Mylan's inequitable conduct defense[141].

---

[140] Forest and Merz alleged that Mylan voluntarily withdrew the Expert Report of Cameron K. Weiffenbach regarding patent term extension allegations on December 7, 2009. Pretrial Order, Exhibit 11, ¶ 242 n. 5.

Likewise, Mylan acknowledged that it voluntarily withdrew the Weiffenbach Report but maintained its contention that the '703 patent term extension was invalid and unenforceable. Pretrial Order, Exhibit 12, ¶ 199 n. 9.

346. In response, Mylan would have argued that it was not alleging inequitable conduct. Rather, it was arguing that material violations of the requirements 35 U.S.C. § 156 were sufficient to invalidate a patent term extension. On May 8, 2009, Mylan filed its Second Amended Answer and Counterclaims in which it pleaded that "[t]he patent term extension for the '703 patent is invalid due to a material failure to comply with the requirements of 35 U.S.C. § 156." Second Amended Answer and Counterclaims, ECF No. 322, ¶ 107.

347. As noted previously, under 35 U.S.C. § 156, the PTE Applicant must provide certain information for the USPTO and the HHS Secretary to determine the period of extension (35 U.S.C. § 156(d)(1)(C)) and comply with its duty to disclosure material information to the USPTO and the HHS Secretary (35 U.S.C. § 156(d)(4)). In my opinion, Mylan had pleaded as an affirmative defense of invalidity that which it intended to assert at trial under 35 U.S.C. § 156.

348. If *assuming* Forest and Merz were successful in convincing the court that Mylan, in effect, was alleging inequitable conduct (but had not pleaded inequitable conduct), my analysis still would continue.

349. First, a reasonable and competent attorney would know that the District Court may have permitted Mylan to amend its pleadings,[142] for example, to include allegations of inequitable conduct.

350. Second, it is my understanding that around the time the parties entered into settlement discussions, Mylan intended to file an antitrust litigation against Forest and Merz alleging unlawful monopolization on account of their alleged misrepresentations to the USPTO and the FDA during procurement of the PTE Application for the '703 patent. Mylan informed Forest and Merz of Mylan's intentions, and then the parties entered into a "standstill" agreement to provide an opportunity to consider the allegations[143].

---

[141] For completeness, I note that I did not find anywhere in the record where Mylan used the term "inequitable conduct" when asserting a defense. Rather, Mylan asserted a defense that the Patent Term Extension of the '703 patent was invalid or unenforceable due to a Forest and Merz's material failure to comply with 35 U.S.C. §156. Pretrial Order, Exhibit 12, ¶ 15.

[142] A defendant may amend its pleadings to claim inequitable conduct unless the amendment is grounded on bad faith or dilatory motive, or it would unduly prejudice the other party. *Inline Connection Corp. v. AOL Time Warner, Inc.*, 237 F.R.D. 361, 369 (D. Del. 2006).

[143] In a letter agreement ("standstill") dated February 18, 2010, counsel for Mylan and Forest referenced a draft complaint involving antitrust allegations regarding Namenda, which Mylan planned to file against Forest and Merz. FRX-AT-03629655-FRX-AT-03629656. The letter stated, "[t]he intent of this agreement is to provide Mylan and Forest with an opportunity to settle Mylan's allegations against Forest before the [c]omplaint becomes public and preserve the status quo during the times of these discussions." *Id.* at FRX-AT-03629655.

351. Accordingly and in my opinion, a reasonable and competent patent attorney at the time of settlement would have realized that either during the Namenda Litigation or during the antitrust litigation, Mylan would have been able to bring before a court[144] its allegations that Forest and Merz violated their compliance obligations under 35 U.S.C. § 156 by acting in bad faith or by gross negligence, thus, invalidating the patent term extension for the '703 patent. In my opinion, Forest and Merz could not "hide behind a procedural shield" of an alleged "failure to plead."

d. Conclusion

352. To my knowledge, there are very few cases that have been decided in this area of patent law regarding these types of patent term extension issues. To my knowledge, the District Court's consideration of this issue would have been the first time that 35 U.S.C. § 282(c) would have been interpreted by a court. Additionally, to my knowledge, the Namenda Litigation would have been the first time that a court considered the above described 35 U.S.C. § 156 compliance issues relating to failure to provide material information on due diligence activities during prosecution of patent term extension application. In my opinion, the lack of precedent would have created enhanced uncertainty and concern for all parties regarding the outcome of the Namenda Litigation as it related to these issues.

353. Taking all of the above into consideration and in my opinion, a reasonable and competent patent attorney would have realized that it would be difficult to predict the likelihood of success for either party but that Mylan could create precedent and prevail. As a result and in my opinion, the *overall* chance of success was about 50% in favor of Mylan and about 50% in favor of Forest and Merz for Mylan to meet its burden and (1) invalidate the *entire* Certificate of Patent Term Extension of the '703 patent thus returning its expiration date to April 11, 2010, or (2) at least invalidate that portion of the Certificate beyond the originally requested 1,250 day extension, thus reducing its expiration date to September 12, 2013.

C. Noninfringement Defenses

354. 35 U.S.C. § 271(e)(2) establishes that it is an act of infringement to submit an ANDA containing a Paragraph IV certification to the FDA under section 505(j) of the Federal

---

In the draft complaint, Mylan alleged that it "brings this action seeking relief to [Forest's and Merz's] willful and deceptive conduct through which it has extended its monopoly over dementia treatment by approximately 19 months." FRX-AT-03629662 at ¶ 1. Mylan also alleged that Forest and Merz "improperly manipulated the [patent term extension] process through the submission of incorrect information and subsequent knowing misrepresentations to the USPTO" and that "[t]he purpose and effect of this conduct was to unlawfully monopolize the market for Namenda ® and its generic equivalents." FRX-AT-03629663, ¶¶ 3–4.

[144] In other words, either the Delaware District Court would consider the issue or another district court would be asked to consider the issue in the form of Mylan's antitrust allegations against Forest and Merz.

Food, Drug, and Cosmetic Act for a drug claimed in a patent or the use of which is claimed in a patent. This act of infringement includes the submission of an ANDA to the FDA containing a Paragraph IV certification pursuant to section 505(j)[145].

355. "Infringement occurs when a properly construed claim of an issued patent covers an accused device." *DSW, Inc. v. Shoe Pavilion, Inc.*, 537 F.3d 1342, 1346 (Fed. Cir. 2008). "To show infringement of a patent, a patentee must supply sufficient evidence to prove that the accused product or process contains, either literally or under the doctrine of equivalents, every limitation of the properly construed claim." *Seal-Flex, Inc. v. Athletic Track & Court Constr.*, 172 F.3d 836, 842 (Fed. Cir. 1999). Accordingly, "[t]he test for patent infringement requires both proper interpretation of the claim scope and proper comparison of the claims with the accused device." *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1023 (Fed. Cir. 1997).

356. The patent holder has the burden of proving infringement by a "preponderance of the evidence." *Warner-Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1341 n.15 (Fed. Cir. 2005); *see also Amgen Inc. v. F. Hoffman -La Roche Ltd*, 580 F.3d 1340, 1374 (Fed. Cir. 2009).

1. Direct Infringement – Literal Infringement

a. Forest and Merz's Position

357. Forest and Merz's position during the Namenda Litigation was that the proposed use of Mylan's generic product as described in Mylan's ANDA infringed method claims 1-3, 6, 8, 10-12, and 14-19 of the '703 patent. Forest and Merz asserted that Mylan's product package insert for its generic Namenda intentionally encouraged physicians, other healthcare professionals, caregivers and patients to use its generic product in accordance with the methods recited in the above claims. *See, e.g.*, Pretrial Order, Exhibit 11, ¶¶ 45–86; 316–67.

b. Mylan's Position

358. Mylan's position during the Namenda Litigation was that Forest and Merz failed to prove that Mylan's generic product would directly infringe the asserted claims because "[n]one of the evidence presented by [Forest and Merz] (or any other evidence) relating to the administration of Mylan's proposed Memantine Tablets demonstrates that it will be administered in an 'effective amount' so as to cause the 'prevention of an imbalance of neuronal stimulation mechanisms,' 'an antagonistic intervention with regard to the N-methyl-D-aspartate [NMDA] receptor channels,' or 'an antagonistic intervention with

[145] *See* 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV).

regard to the excessive inflow of calcium through NMDA receptor channels after Alzheimer's disease.'" Pretrial Order, Exhibit 12, ¶ 90.

c. Analysis

359. The asserted independent claims of the '703 patent following reexamination recite, in part:

Claim	Claim Language
1	A method for the prevention or treatment of cerebral ischemia comprising the step of orally administering, to a patient diagnosed with Alzheimer's disease and in need thereof, an effective amount of an adamantane derivative of the general formula . . . .
14	A method for the treatment of cerebral ischemia comprising orally administering to a patient diagnosed with Alzheimer's disease and in need of such treatment an effective amount of an adamantane derivative of the general formula . . . .
17	A method for the treatment of an imbalance of neuronal stimulation after Alzheimer's disease, comprising orally administering to a patient diagnosed with Alzheimer's disease and in need of such treatment an effective amount of an adamantane derivative of the general formula . . . .

360. As noted in Exhibit K, the District Court construed the following relevant terms from these claims as follows:

Term	Construction
prevention . . . of cerebral ischemia	prevention of an imbalance of neuronal stimulation mechanisms
treatment of cerebral ischemia	an antagonistic intervention with regard to the N–methyl–D–aspartate [NMDA] receptor channels
imbalance of neuronal stimulation after Alzheimer's disease	a pathophysiological situation characterized by an excessive inflow of calcium through the NMDA receptor channels after Alzheimer's disease
treatment of imbalance of neuronal stimulation after Alzheimer's disease	an antagonistic intervention with regard to the excessive inflow of calcium through NMDA receptor channels after Alzheimer's disease
effective amount	an amount shown to cause improvement, in comparison to placebo

361. As evidence of infringement of these independent claims, Forest and Merz offered the Expert testimony of Dr. Rachelle S. Doody. Relying on Mylan's Package Insert, Dr. Doody concluded that the accused product would be used in a "method for the prevention or treatment of cerebral ischemia," Doody Report at ¶ 21, and "[a] method for the treatment of an imbalance of neuronal stimulation after Alzheimer's disease." *Id.* at ¶ 73.

362. In support of this opinion, Dr. Doody noted that Mylan's proposed package insert stated:

> '[p]ersistent activation of central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer's disease. Memantine is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist which binds preferentially to the NMDA receptor-operated cation channels.'

Id. at ¶¶ 22, 73 (quoting MYL-040349).

363. Dr. Doody also noted that the proposed package insert states that "'[m]emantine hydrochloride is an orally active NMDA receptor antagonist'" and that '[m]emantine hydrochloride is a low to moderate affinity uncompetitive NMDA antagonist.'" *Id.* at ¶ 23 (quoting MYL-040348, 375).

364. The proposed package insert, upon which Dr. Doody relied however, does *not* state that memantine hydrochloride tablets are indicated to prevent or treat cerebral ischemia or treat an imbalance of neuronal stimulation after Alzheimer's disease, as construed these terms are by the District Court. Instead, the package insert states that "[m]emantine hydrochloride tablets, USP are indicated for the treatment of moderate to severe dementia of the Alzheimer's type." Mylan Package Insert at MYL-040392.

365. Dr. Doody apparently concluded that the claimed method is nonetheless performed because the package insert states that "[p]ersistent activation of [NMDA] receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer's disease" and "Memantine is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist . . . ." Doody Report at ¶¶ 22, 73 (quoting MYL-040349). In other words, Dr. Doody apparently concluded that the claimed method for treating cerebral ischemia (an antagonistic intervention with regard to the N–methyl–D–aspartate (NMDA) receptor channels) was performed because it is postulated that memantine itself acts as an NMDA receptor antagonist. It is notable that word "postulate" means "to assume or claim as true, existent, or necessary."[146] It does not mean "to prove."

366. With respect to "effective amount", Dr. Doody analyzed that claim element based on the understanding that "this element requires patients being treated for Alzheimer's disease

[146] *Postulate*, Merriam-Webster Online Dictionary. 2017. https://www.merriam-webster.com/dictionary/postulate (last visited August 9, 2017).

with memantine (or another compound covered by the claim) to be advantaged in comparison to patients receiving a placebo." Doody Report at ¶ 30. With this understanding, Dr. Doody concluded that Mylan's generic product was "an effective amount" because according to the package insert "[o]ral administration to patients of memantine hydrochloride at daily dosages of 10 mg and 20 mg has been shown in clinical studies to benefit global performance, cognition, and function in comparison to placebo treatment." *Id.* at ¶ 32 (citing MYL-040353-364). Dr. Doody apparently concluded that Mylan's generic product would be administered in an "effective amount" because when administered to Alzheimer's patients the patients receive a benefit compared to placebo.

367. In response to Dr. Doody's analysis, Mylan offered the rebuttal expert report of John Olney, M.D. Dr. Olney observed that Dr. Doody's infringement analysis relied on the interpretation that "an effective amount of" refers to an amount effective for treating Alzheimer's disease. Olney Rebuttal Report at ¶ 65. Dr. Olney observed that Dr. Doody's interpretation of the independent method claims was incorrect. *Id.* Dr. Olney opined that from the plain language of the claims, the "effective amount of" referred to in claims 1, 14 and 17 is directed to "the prevention or treatment of *cerebral ischemia*" or "the treatment of an *imbalance of neuronal stimulation* after Alzheimer's disease" as construed by the court. *Id.* (emphasis added). In other words, these independent claims are directed to the treatment of cerebral ischemia or imbalances in neuronal stimulation[147].

368. Dr. Olney's opinion is confirmed by his reviewing original independent claim 1, which recited:

> [a] method for the prevention or treatment of cerebral ischemia comprising the step of administering, to a patient in need thereof, an effective amount of an adamantane derivative of the general formula . . . .

See Exhibit F, Claim 1.

369. As seen above, original claim 1 made no reference to Alzheimer's disease. *Id.* And, the reference to "an effective amount of" in the claim is in relation to "the prevention or treatment of cerebral ischemia." *Id.*

[147] I note that that dependent claim 10 of the '703 patent recites "A method according to claim 1 for the treatment of Alzheimer's disease . . . ." But, as a dependent claim, claim 10 must include all the limitations of claim 1. Thus, in my opinion, claim 10 is directed to the "treatment of cerebral ischemia." And, as to infringement of dependent claims "[i]t is axiomatic that dependent claims cannot be found infringed unless the claims from which they depend have been found to have been infringed." *Wahpeton Canvas Co., Inc. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989).

370. From Dr. Olney's research on memantine, he concluded that "the levels of memantine hydrochloride administered to a patient will not approach levels necessary to prevent an imbalance of neuronal stimulation mechanisms, *i.e.*, antagonize the ''persistent activation' of the NMDA receptors', or act as an antagonist at NMDA receptor channels." Olney Rebuttal Report at ¶ 66.

371. In my opinion, for the following reasons, Forest and Merz's proofs on infringement were insufficient to meet their burden for the District Court to find infringement.

372. Forest and Merz's proofs relied on an interpretation of the claims that "an effective amount of" only required showing that "patients being *treated for Alzheimer's disease* with memantine (or another compound covered by the claim) to be advantaged in comparison to patients receiving a placebo." Doody Report at ¶ 30 (emphasis added). In my opinion, however, this approach misapplies the court's claim construction.

373. After Forest and Merz presented their case on infringement and closed their case in chief, in my opinion, Mylan would have likely moved for judgment as a matter of law on the grounds that Forest and Merz's proof of infringement was not based on the proper application of the court's construction of the term "an effective amount."[148]

374. In particular, proof of infringement would have required Forest and Merz to provide evidence that oral administration of the memantine dose proposed in Mylan's ANDA had been shown to cause improvement in *NMDA receptor channel antagonism* when compared to placebo.

375. Forest and Merz did not provide this proof. Instead, through Dr. Doody, Forest and Merz merely referenced Mylan's proposed package insert that "daily dosages of 10 mg and 20 mg has been shown in clinical studies to benefit global performance, cognition, and function in comparison to placebo treatment." Doody Report at ¶ 32. Dr. Doody, however, did *not* identify any evidence showing, for example, that daily dosages of 10 mg and 20 mg have been shown in humans to antagonize NMDA receptor channels when compared to placebo. *See id.* Instead, Dr. Doody relied solely on a passage from Mylan's proposed package insert, which states that it is "hypothesized" or "postulated" that memantine provides a therapeutic effect as an NMDA receptor antagonist. *See id.* at ¶¶ 22, 73. Dr. Malinow's untimely supplemental report did not correct this defect.

[148] In saying this, I recognize that Dr. Malinow submitted an untimely supplemental report seeking to prove that memantine did, in fact, act through a mechanism of action involving the antagonism of NMDA receptors. However, even if his untimely report was not stricken and his opinions were accepted, he offered no evidence that placebo-controlled studies had "shown" memantine to operate by that mechanism of action, as required by the court's construction of "effective amount."

376. In my opinion, Mylan would have also likely moved for judgment as a matter of law on the grounds that Forest and Merz did not provide any testing or data showing that orally administered memantine antagonized NMDA receptor channels when compared to placebo. Instead, Forest and Merz's expert cited to a hypothesis recited in a package insert. *See Boston Sci. Scimed, Inc. v. Cordis Corp.*, 483 F. Supp. 2d 390, 396 (D. Del. 2007) (finding noninfringement and discrediting the plaintiff's expert's opinion on infringement for relying on a hypothesis instead of performing actual testing and noting that "the court is not confident at this juncture that [the plaintiff's] hypothesis passes muster under *Daubert*").

377. In my opinion and for the above reasons, Forest and Merz would not have proved that Mylan infringed independent claims 1, 14, and 17. As a result, a reasonable and competent patent attorney would have recognized that a court could have granted Mylan's motion for judgement as a matter of law.

378. As to infringement of the asserted dependent claims "[i]t is axiomatic that dependent claims cannot be found infringed unless the claims from which they depend have been found to have been infringed." *Wahpeton Canvas Co., Inc. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). Thus, Forest and Merz would have also failed to prove that Mylan infringed asserted dependent claims 2-3, 6, 8, 10-12, 15-16, and 18-19 of the '703 patent.

d. Conclusion

379. In my opinion, a reasonable and competent patent attorney would have realized at the time of settlement that that Forest and Merz might be found to not have met their burden of proof of showing that Mylan directly infringed claims 1-3, 6, 8, 10-12, and 14-19 of the '703 patent[149].

380. Based on the above and in my opinion, a reasonable and competent patent attorney would have realized that each party's chance of success on the noninfringement defense was about 50% in favor of Mylan to about 50% in favor of Forest and Merz, for Forest and Merz to prove that the administration of Mylan's product in the amounts set forth in Mylan's proposed package insert would directly infringe the asserted claims of the '703 patent.

[149] In her Report, Dr. Doody stated that "any claim that is found not to be infringed literally is nonetheless infringed under the doctrine of equivalents." Doody Report at ¶ 96. It was, however, Forest and Merz's burden to prove infringement under the doctrine of equivalents and they never asserted a viable theory.

2. Indirect Infringement – Induced Infringement

381. Section § 271(b) provides that "[w]hoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). To prevail on a claim for inducement pursuant to § 271(b), "'the patentee must establish 'first that there has been direct infringement, and second that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement.'" *ACCO Brands, Inc. v. ABA Locks Mfrs. Co.*, 501 F.3d 1307, 1312 (Fed. Cir. 2007) (quoting *Minn. Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1304–05 (Fed. Cir. 2002)).

a. Forest and Merz's Position

382. Forest and Merz's position during the Namenda Litigation was that Mylan would be liable for actively inducing infringement if it "sold or marketed" the product as described in its ANDA because Mylan's proposed package insert "intentionally encourage[d] physicians, other healthcare professionals, caregivers, and patients to use" Mylan's generic product "in accordance with the methods of use recited in claims 1-3, 6, 8, 10-12, and 14-19 of the '703 patent." Pretrial Order, Exhibit 11, ¶ 368; *see also id.* at ¶¶ 45–87.

b. Mylan's Position

383. Mylan's position during the Namenda Litigation was that its product would not indirectly infringe any of the asserted claims of the '703 patent because its product would "not be administered in a manner that [would] directly infringe any asserted claim of the '703 patent." Pretrial Order, Exhibit 12, ¶ 115. Mylan also argued that it "lack[ed] the requisite knowledge that any customer [would] directly infringe the '703 patent" and that it had "not taken any affirmative steps to actively encourage consumers to directly infringe any claim of the '703 patent." *Id.* at ¶ 117.

c. Analysis

384. Induced infringement first requires a finding of direct infringement. *See ACCO Brands, Inc.*, 501 F.3d at 1312. In my opinion, for the reasons stated above, the District Court could have found that Forest and Merz failed to prove that Mylan directly infringed the claims of the '703 patent and, consequently, Forest and Merz would be unable to prevail on their claims that Mylan infringed the claims of the '703 patent by inducement.

d. Conclusion

385. In my opinion, a reasonable and competent patent attorney would have realized at the time of settlement that the District Court could have found that Forest and Merz failed to prove Mylan directly infringed the claims of the '703 patent. Consequently, Forest and

Merz would have been unable to prevail on their assertions that Mylan infringed claims 1-3, 6, 8, 10-12, and 14-19 of the '703 patent by induced infringement.

386. Because *indirect* infringement (*i.e.*, induced infringement and contributory infringement) requires Forest and Merz to prove *direct* infringement (Report, Paragraph 381), a reasonable and competent patent attorney would have realized that each party's chance of success on noninfringement remained at about 50% in favor of Mylan to about 50% in favor of Forest and Merz, for Forest and Merz to prove that Mylan directly or indirectly infringed (*i.e.*, by inducement) the asserted claims of the '703 patent.

3. Indirect Infringement – Contributory Infringement

387. "Contributory infringement prohibits the importation into the United States of a component or apparatus for use in a patented process that has no use except through practice of the patented method." *Alloc, Inc. v. Int'l Trade Cmm'n*, 342 F.3d 1361, 1374 (Fed. Cir. 2003).

a. Forest and Merz's Position

388. Forest and Merz's position during the Namenda Litigation was that Mylan would be liable for contributory infringement if it "sold or marketed" the product as described in its ANDA because Mylan's proposed products "are especially adapted for use in connection with the methods of Claims 1-3, 6, 8, 10-12, and 14-19 of the '703 patent" and because Mylan could not "meet its burden of proving that there are any substantial noninfringing uses" for its generic product. Pretrial Order, Exhibit 11, ¶ 369; *see also id.* at ¶¶ 45–88.

b. Mylan's Position

389. Mylan's position during the Namenda Litigation was that its product would "not contributorily infringe any claim of the '703 patent." Pretrial Order, Exhibit 12, ¶ 116. Mylan argued that its product "is a staple product that has substantial noninfringing uses." *Id.*

c. Analysis

390. As with induced infringement, liability "for contributory infringement is dependent upon the existence of direct infringement." *Joy Tech., Inc. v. Flakt, Inc.*, 6 F.3d 770, 774 (Fed. Cir. 1993). In my opinion and for the reasons stated above, the District Court could have found that Forest and Merz failed to prove that Mylan directly infringed the claims of the '703 patent. Consequently, Forest and Merz would have been unable to prevail on their claims that Mylan infringed the asserted claims of the '703 patent by contributory infringement.

d. Conclusion

391. In my opinion, a reasonable and competent patent attorney would have realized at the time of settlement that a court could have found that Forest and Merz failed to prove Mylan directly infringed the claims of the '703 patent. Consequently, Forest and Merz could be unable to prevail on their assertions that Mylan infringed claims 1-3, 6, 8, 10-12, and 14-19 of the '703 patent by induced infringement.

392. Because *indirect* infringement (*i.e.*, induced infringement and contributory infringement) require Forest and Merz to prove *direct* infringement (Report, Paragraph 381), a reasonable and competent patent attorney would have realized that each party's chance of success on the noninfringement defense remained at about 50% in favor of Mylan to about 50% in favor of Forest and Merz, for Forest and Merz to prove that Mylan directly or indirectly (*i.e.*, by contributory infringement) infringed the asserted claims of the '703 patent.

XII. ANALYSIS OF PERCEIVED LIKELIHOOD OF SUCCESS

A. Perceived Likelihood of Success Based on Statistical Analyses Available in 2009 – 2010 Era

393. As described in Section X above, a reasonable and competent patent attorney asked to evaluate the parties' likelihood of success in the Namenda Litigation would start from an understanding position that it is difficult for a patent holder to overcome invalidity challenges and simultaneously prove infringement at trial. From statistical sources available in 2009–2010, the patent attorney would have understood that statistically, on average, a patent litigation defendant had approximately a 65 to 75% chance of success. And as explained above, viewed conservatively, the statistics show that, on average, a patent litigation defendant had at least a 60% chance of success. *See* Section X. Based upon my review of Mylan's defenses – presented above – it is my opinion that Mylan's case was stronger than the average accused infringer's case. Accordingly, it is my opinion that speaking conservatively Mylan's likelihood of success was greater than 60%.

B. Perceived Likelihood of Success Based on Independent Analysis of the Merits

394. For many parties, the above kind of general statistical assessment would *not* be sufficient for them to make a decision. Parties would expect a reasonable and competent patent attorney to analyze the set of issues and facts unique to the specific patent litigation and asserted patent(s) that need to be considered on an individual basis (*e.g.*, actual defenses being alleged, claim language and scope, and ability to "engineer around" claim

language). Thus, the merits of the Namenda Litigation also should be evaluated when considering the chance of success.

395. A summary of my positons on the merits is found in the below Table:

Summary Table		
Defense	**Reason(s)**	**Section**
Anticipation (§ 101)	Mylan met its burden of demonstrating that the Memantine Studies anticipate the asserted '703 claims. Because the size of the genus of the patient population in certain of the Memantine Studies was very small (*i.e.*, dementia), one skilled in the art would envisage each member of this limited class and recognize that patients with Alzheimer's disease would be a member of that group. Moreover, an internal Merz memo acknowledged that "[a]ll patients participating in the [Tempel (*i.e.*, a Memantine Study)] study suffered from organic brain syndrome … resulting from Alzheimer's disease or cerebral sclerosis."	II.B.1
Obviousness (§ 103)	If Mylan did not prevail with its anticipation defense, Mylan presented a strong showing that the claimed subject matter was prima facie obvious. The Memantine Studies describe successful oral administration of memantine to an elderly patient population suffering from dementia and OBS. To the extent that Forest and Merz may have argued that these four references do not expressly use the words "Alzheimer's disease" to describe the patients' diagnosis, this conclusion would have been obvious to a skilled artisan, for example in view of the Fleischhacker reference. Once this prima facie case of obviousness were established, a reasonable and competent patent attorney would have recognized that it would be difficult for Forest and Merz to overcome this prima facie case of obviousness through secondary considerations.	II.B.2
Enablement (§ 112) "Unproven Hypothesis" (Mechanism of Action)	Mylan met its burden of demonstrating that the disclosure in the '703 patent was legally insufficient to teach a skilled artisan how to use the asserted method of treatment claims. Forest and Merz's reliance on a hypothesis was not enough for satisfying enablement. The '703 patent proposed an unproven *hypothesis* that because	II.B.3.a.

Summary Table		
Defense	**Reason(s)**	**Section**
	memantine exhibits activity as an NMDA antagonist, it *may* be useful in treating Alzheimer's disease via NMDA receptor antagonism. Mylan demonstrated that at the relevant time a skilled artisan would not have accepted this hypothesis.	
Enablement (§ 112) "Effective Amount"	Mylan met its burden of demonstrating that at the relevant time the term "effective amount" was not enabled over the full scope of this broadly claimed dose range of "about 0.01 to 100 mg/kg" (*i.e.*, 0.8 mg to 8.9 g). Mylan demonstrated that at the relevant time a skilled artisan would not have concluded that the Experiments in the '703 patent with memantine were indicative of an ability to treat Alzheimer's disease in diagnosed patients. Moreover, Mylan demonstrated that the claimed dosage range was much broader than that found in these Experiments.	II.B.3.b.
Patent Term Extension (§ 156)	Mylan met its burden of demonstrating that Forest and Merz did not comply with their obligations under 35 U.S.C § 156. During the pendency of the PTE Application, Forest and Merz failed to update the USPTO and the HHS Secretary about the number days within the *expanded* testing phase regarding their due diligence and thus violated their obligation to provide material information under 35 U.S.C § 156. Forest and Merz knew or should have known that the USPTO in its determination for patent term extension credited Forest and Merz for being diligent during the full duration of the expanded testing period because the USPTO relied on the representations on due diligence made in Forest and Merz's originally filed PTE Application. Forest and Merz knew or should have known that the missing information on due diligence during the full expanded testing phase was material to the USPTO's patent term extension calculation for the '703 patent and thus violated its duty of disclosure obligation under 35 U.S.C § 156 by exhibiting bad faith or gross negligence.	II.B.4.
Noninfringement (§ 271)	Forest and Merz did not meet their burden to present evidence that Mylan's proposed memantine tablets would be orally administered in an 'effective amount' to a patient diagnosed with Alzheimer's disease so as to prevent or treat *cerebral ischemia* or treat an *imbalance of neuronal stimulation* after	II.C.

Summary Table		
Defense	**Reason(s)**	**Section**
	Alzheimer's disease. The court's construction of the term "effective amount" required Forest and Merz to prove that orally administered memantine at the dose proposed by Mylan had been shown to act as an NMDA antagonist compared to placebo. Although relying on Mylan's proposed package insert, Forest and Merz did not present evidence to this effect.	

396. To prevail on any of their asserted claims, Forest and Merz would have been required to survive all of Mylan's above anticipation challenges under 35 U.S.C. § 102, obviousness under 35 U.S.C. § 103, and enablement challenges under 35 U.S.C. § 112. Forest and Merz also would have to prevail in showing the Mylan's method of using its generic product infringed an asserted claim of the '703 patent.

397. As noted above (Report, Paragraph 350), Mylan also had threatened Forest and Merz with an antitrust action because of the way they prosecuted the patent term extension application for Namenda. As a result and in my opinion, Forest and Merz also would have been required to survive Mylan's attack of their patent term extension during the antitrust action which is based on their alleged failure to comply their duty of disclosure obligations under 35 U.S.C. § 156.

398. For all of the reasons set forth in Section XI above, a reasonable and competent patent attorney, who was fully apprised of the above-described fundamental aspects of the dispute between the litigants, in my opinion, would have made the conclusions regarding the likelihood of success through trial and appeal based on the merits of the case as described in the below table.

Defenses		**% Likelihood of Success**	
		Mylan	**Forest and Merz**
Invalidity	Anticipation (§ 102)	55	45
	Obviousness (§ 103)	45	55
	Enablement (§ 112) "Unproven Hypothesis" (Mechanism of Action)	60	40
	Enablement (§ 112) "Effective Amount"	60	40
Noninfringement (§ 271)		50	50

399. As noted above, Mylan would have been successful based on prevailing under any one of the above invalidity defenses or its noninfringement defenses. For example, Mylan could

have prevailed in the litigation by only succeeding on the "Enablement – 'Unproven Hypothesis (Mechanism of Action)'" defense, yet not succeeded on any of the other defenses. Thus, in my opinion the conservative view of Mylan's likelihood of success based on its single strongest defense is 60% or higher.

400. Accordingly, it is my opinion that a reasonable patent attorney would have concluded conservatively that Mylan's *overall* chance of success at the time of settlement of the Namenda Litigation was greater than 60% through trial and appeal based on the merits[150]. Further, a reasonable patent attorney would have concluded that Forest and Merz's chance of success was less than 40% through trial and appeal based on the merits[151, 152].

401. Moreover, based on Mylan's assertions that Forest and Merz did not comply with the requirements of 35 U.S.C. § 156 ("**PTE Assertions**"), Mylan alternatively (or in addition to its above invalidity and noninfringement defenses) could have been successful in invalidating at least a portion of the term (or the entire term) of the Certificate of Patent Term Extension of the '703 patent. As discussed previously, in my opinion, a reasonable and competent patent attorney would have concluded that Mylan's chance of success for prevailing with its PTE Assertions at the time of settlement of the Namenda Litigation

[150] In providing this opinion, I have taken a conservative approach regarding the overall chance of success for Mylan by basing my opinion only on Mylan's chance of success on its strongest defense. If a reasonable and competent patent attorney were to take into consideration the fact that Mylan needed to prevail on any one of the above issues, then Mylan's overall chance of success would be greater than 60%. And, thus, Forest and Merz's overall chance of success would be less than 40%.

[151] For completeness, I note that, in my opinion, the at least 60% *overall* chance of success for Mylan based on the merits of the case does not differ significantly from the lower level of the statistically derived 65-75% overall chance of success for a generic company defendant. My assessment of Mylan's likelihood of success is conservative. As I have explained, in my opinion the strength of Mylan's case was better than the average accused infringer's case.

[152] From my experience, some patent attorneys would make a further calculation relating to the overall likelihood of success by combining the likelihood of success for the individual issues. That is, calculate the overall probability of a party prevailing by multiplying the probability of success on each issue. To prevail on any of the asserted claims of the '703 patent, Forest and Merz would have been required to survive the anticipation challenge, the obviousness challenge, both enablement challenges (hypothesis and "effective amount") and the noninfringement challenge. If a reasonable and competent patent attorney would have given Forest and Merz a 45% likelihood of success on surviving the anticipation challenge, 55% likelihood of success on surviving the obviousness challenge, a 40% likelihood of success of surviving the enablement (unproven hypothesis) challenge, a 40% likelihood of success on surviving the enablement (effective amount) challenge, and 50% a likelihood of success on Mylan's noninfringement defense, Forest and Merz's overall likelihood of success would have been 1.98% based on the above approach.

In my experience, reasonable and competent patent attorneys do not typically offer this kind of precision in their estimates, and instead tend to offer numbers rounded to the nearest 5% or 10%. And, based on that approach, Forest and Merz would have had about an overall 5 to 10% chance of success of prevailing on the asserted claims of the '703 patent. Stated conversely, Mylan would have had an overall 90 to 95% chance of success on invalidating the asserted claims based on this approach.

was about 50% through trial and appeal based on the merits. Conversely, a reasonable patent attorney would have concluded that Forest and Merz's chance of successfully defending against Mylan's PTE Assertions was about 50% through trial and appeal based on the merits.

XIII. REASONABLE CONCLUSIONS REGARDING LITIGATION TIMING

402. I was asked to estimate the expected length of the Namenda Litigation had the parties not settled.

403. Based on my review of the key deadlines and events during the Namenda Litigation as summarized in Exhibit L, together with my experience as a patent attorney, I have estimated the likely timeline for the remaining stages of the Namenda Litigation and the timeline for an appeal to the Federal Circuit.

404. For purposes of this Report, I established as my starting point for the calculations as if a trial on the merits would have been held on April 5, 2010, as scheduled, and that the trial would have lasted one week[153].

405. Based on my experience, it would have taken the District Court about 3 to 6 months to issue an opinion on the matter once trial was completed. Further, based on my experience, the filing with the District Court of a notice of appeal and the filing and docketing of an appeal at the Federal Circuit would have been completed within 1 to 2 months thereafter. In other words, a party could have filed and had an appeal docketed, should it choose to do so, from 4 to 8 months after the completion of the District Court trial. In my opinion, a reasonable and competent patent attorney likely would have concluded that, absent settlement, the District Court in the Namenda Litigation would have entered a final judgment as early as July 2010 and as late as October 2010.

406. Regarding the time during an appeal, the Federal Circuit keeps a record of data that shows the "Median Time to Disposition in Cases" on the merits from "Docketing Date to Disposition Date."[154] A review of the Federal Circuit's data from FY 2011 shows that the median time for resolution of appeals arising from district court cases, which would include Hatch-Waxman patent infringement cases, was 11.2 months.

---

[153] *See* Scheduling Order, ECF No. 114 (stating "[t]his matter is scheduled for a five-day bench trial on a date to be determined."); *see also* Supplemental Scheduling Order, ECF No. 117 (setting April 5, 2010 to April 9, 2010 as trial dates).

[154] United States Court of Appeals for the Federal Circuit, *Median Time to Disposition of Cases Terminated After Hearing or Submission*, (FY 2007–2016), http://www.cafc.uscourts.gov/sites/default/files/the-court/statistics/FY16_Median_Disposition_Time_for_Cases_Terminated_after_Hearing_or_Submission_Detailed_Table_of_Data_2.pdf (last visited July 18, 2017).

407. In my opinion, an appeal in the Namenda Litigation would not have been any more complex than the median patent infringement case reviewed by the Federal Circuit. For example, some patent infringement cases involve multiple patents which increase their complexity. The Namenda Litigation, however, involved only one patent.

408. Accordingly, in my opinion, a reasonable and competent patent attorney would have expected that once docketed, an appeal at the Federal Circuit for the Namenda Litigation would have been decided in approximately 11 months. Thus, a decision by the Federal Circuit would have occurred between about July 2011 and November 2011 – which is between about 15 and 19 months after the conclusion of the District Court trial.

409. A party has 14 days from entry of judgment in a Federal Court decision to file a petition for a panel Rehearing. *See* FED. R. APP. P. 40. Should a party request a Rehearing or an en banc Rehearing, in my opinion, a reasonable and competent patent attorney would have expected a decision from the Federal Circuit with respect to the Rehearing petition in approximately 1 to 2 months[155]. Thus, in the Namenda Litigation, a decision on a Rehearing petition would have occurred between September 2011 and January 2012, which is between about 17 and 21 months after the conclusion of the District Court trial.

410. I would not expect a party to be successful in pursuing a petition for Rehearing to the Federal Circuit because the Federal Circuit grants very few Rehearing petitions each year[156]. Should a Rehearing or an en banc Rehearing occur, in my opinion, a reasonable and competent patent attorney would have expected that the Namenda Litigation would have been resolved in approximately 7 to 12 additional months after the Federal Circuit's grant of the petition for Rehearing[157]. Thus, a decision after Rehearing by the Federal Circuit would have occurred between about April 2012 and January 2013, which is between about 24 and 33 months after the conclusion of the District Court trial.

411. Likewise, I would also not expect a party to be successful in pursuing a petition for certiorari to the Supreme Court because it takes very few cases each year for review[158].

---

[155] For the calculations, I assumed about 2 months for the total time mentioned in this paragraph.

[156] An en banc rehearing at the Federal Circuit is especially rare. The Federal Circuit's en banc cases represent 0.10% of the total number of cases terminated from 1982-2010 and 0.18% of cases terminated from 1998-2009. R. Vacca, *Acting Like an Administrative Agency: The Federal Circuit En Banc*, 76 Mo. L. Rev. 733, 736 (2011) (considering cases terminated from 1982-2010); C. Cotropia, *Determining Uniformity within the Federal Circuit by Measuring Dissent and En Banc Review*, 43 Loy. L.A. L. Rev. 801, 817 (2010) (considering cases terminated from 1998-2009).

[157] That is, about 6 to 9 months until a Rehearing and about 1 to 3 months until a Federal Circuit Decision after Rehearing.

[158] According to the *Reporter's Guide to Applications Pending Before The Supreme Court of the United States*, the Supreme Court receives approximately 7,000-8,000 petitions for a writ of certiorari each Term. The Supreme Court grants and hears oral argument in about 80 cases (*i.e.*, about 1%).

For completeness, however, I note that following an adverse Federal Circuit Decision after a rehearing in the Namenda Litigation, a party would have 90 days after entry of the Federal Circuit judgment or a denial of Rehearing petition to file a petition for a writ certiorari to the Supreme Court. *See* SUP. CT. R. 13. It then takes approximately 6 weeks[159] for the Supreme Court to grant or deny a certiorari petition[160].

412. Should a petition for certiorari (after a denial of a petition for Rehearing by the Federal Circuit) be *denied*, in my opinion, a reasonable and competent patent attorney would have expected that the Namenda Litigation would have been resolved approximately between January 2012 and June 2012, which is between about 21 and 26 months after the conclusion of the District Court trial.

413. Should the certiorari petition be *accepted* between about August 2012 and June 2013, in my opinion, a reasonable and competent patent attorney would have expected a Supreme Court decision by February 2013 or October 2014[161], which is between about 34 and 54 months after the conclusion of the District Court trial.

---

https://www.supremecourt.gov/publicinfo/reportersguide.pdf at pp. 15-16 (last visited Aug. 30, 2017) ("**Reporter's Guide**").

During the time of settlement of the Namenda Litigation, the Supreme Court granted review to 0.9% of cases during the 2011 term (3.7% from the Appellate Docket (which consists of all paid cases, including those arising from the Federal Circuit) and 0.1% from the Miscellaneous Docket (which consists of all cases filed *in forma pauperis*), *The Statistics*, 126 Harv. L. Rev. 388, 395 (2012); 1.2% of cases during the 2012 term (5.4% from the Appellate Docket and 0.2% from the Miscellaneous Docket), *The Statistics*, 127 Harv. L. Rev. 408, 416 (2013); and 1.0% of cases during the 2013 term (4.2% from the Appellate Docket and 0.1% from the Miscellaneous Docket). *The Statistics*, 128 Harv. L. Rev. 401, 409 (2014).

[159] For the calculations, I have assumed 1 to 2 months.

[160] Reporter's Guide at p. 16.

[161] I was not able to find any statistics regarding average decision pending times at the Supreme Court. A call to the Supreme Court's Public Information Office revealed the following: If a certiorari petition is granted during the first half of the Supreme Court Term (*i.e.*, between October and January), a decision is usually issued within that term (*i.e.*, from October to late June/early July). If a certiorari petition is granted during the second half of the term (*i.e.*, between February and late June), a decision is usually issued during the following term. *See also* Reporter's Guide at p. 16 (providing "Cases granted after mid-January are typically carried over until the next term begins the following October, unless the case is expedited by the Court").

Based on my calculations, a certiorari petition could have been granted between about August 2012 to June 2013. As a result, one might expect a Supreme Court decision by June 2013 – June 2014.

414. The above time estimates are summarized in the below Tables:

Tables - Approximate Time from End of Trial through Appeal in the Namenda Litigation

Assuming Denial of Federal Circuit Request for Rehearing and Denial of Petition for Certiorari			
Action	**Estimated Time**	**Total Estimated Time (From Trial)**	**Estimated End Date (From Trial)**
Trial	~ 5 days		April 2010
District Court Decision	**~ 3 to 6 months**	**~ 3 to 6 months**	**July 2010 – Oct 2010**
Docketing of Appeal	~ 1 to 2 months	~ 4 to 8 months	Aug 2010 – Dec 2010
Federal Circuit Decision	~ 11 months	~ 15 to 19 months	July 2011 – Nov 2011
Time from Trial to Federal Circuit Decision		**~ 15 to 19 months**	**July 2011 – Nov 2011**
Request for Federal Circuit Rehearing with Denial	~ 2 months	~ 17 to 21 months	Sept 2011 – Jan 2012
Time from Trial to Federal Circuit Decision with Denial of Rehearing		**~ 17 to 21 months**	**Sept 2011 – Jan 2012**
Petition for Certiorari filed and Denied	~ 4 to 5 months	~ 21 to 26 months	Jan 2012 – June 2012
Time from Trial through Federal Circuit Decision, Denial of Rehearing, and Denial of Certiorari petition		**~ 21 to 26 months**	**Jan 2012 – June 2012**

Assuming Grant of Federal Circuit Request for Rehearing and Grant of Petition for Certiorari			
Action	**Estimated Time**	**Total Estimated Time (From Trial)**	**Estimated End Date (From Trial)**
Trial	~ 5 days		April 2010
District Court Opinion	~ 3 to 6 months	**~ 3 to 6 months**	**July 2010 – Oct 2010**
Docketing of Appeal	~ 1-2 months	~ 4 to 8 months	Aug 2010 – Dec 2010
Federal Circuit Decision	~ 11 months	~ 15 to 19 months	July 2011 – Nov 2011
Time from Trial to Federal Circuit Decision		**~ 15 to 19 months**	**July 2011 – Nov 2011**
Request for Federal Circuit Rehearing	~ 2 months	~ 17 to 21 months	Sept 2011 – Jan 2012
Federal Circuit Decision with Decision on Rehearing	~ 7 to 12 months	~ 24 to 33 months	April 2012 – Jan 2013
Time from Trial to Federal Circuit Decision with Decision on Rehearing		**~ 24 to 33 months**	**April 2012 - Jan 2013**
Petition for Certiorari filed and Granted	~ 4 to 5 months	~ 28 to 38 months	Aug 2012 – June 2013
Supreme Court Decision Issued	*See* Report, Footnote 161		June 2013 - June 2014
Time from Trial through Federal Circuit Rehearing, Certiorari being granted and Supreme Court Decision			**June 2013 - June 2014**

415. Regarding a possible remand by the Federal Circuit to the District Court, in the previously noted FTC Study (Report, Paragraph 87), the FTC found that in 13 of 14 decisions in which the brand-name company appealed an adverse district court decision, "the U.S. Court of Appeals for the Federal Circuit affirmed district court decisions of patent invalidity or non-infringement." FTC Study at 21. In the one remaining appeal, there were two patents at issue, and the Federal Circuit reversed on one and affirmed on the other. *Id.* The reversed patent was not remanded for a second trial. *Id.* Based on the above data, in my opinion, a reasonable and competent patent attorney would have expected that the likelihood of a remand for a second trial would be remote.

416. In summary and in my opinion, it is more likely than not that a three-judge appellate decision would issue from the Federal Circuit between July 2011 and November 2011. Furthermore, in my opinion it is more likely than not that a remand would not be required and that subsequent petitions for (1) rehearing or rehearing *en banc* and (2) *certiorari* would be denied. Based upon the timelines provided herein, it therefore is my opinion that the appeal would become final between January 2012 and June 2012.

XIV. REASONABLE CONCLUSIONS REGARDING LITIGATION COSTS

417. I was asked to estimate the cost savings a reasonable and competent patent attorney would anticipate that Forest/Merz, and Mylan saved as a result of their settlement in the Namenda Litigation.

418. My estimate is based upon three sources of information. First, I have estimated the litigants' saved litigation costs based on my personal experience coupled with the key remaining deadlines and events for the Namenda Litigation. Second, I have reviewed AIPLA Survey data (Report, Paragraphs 422-426), which assemble historical typical costs of patent infringement litigation. Third, I have reviewed a litigation cost estimate dated March 23, 2009 that was provided to Forest/Merz from their counsel Kirkland & Ellis[162].

419. My Experience as Chief Patent Counsel. First, as mentioned in Section II and Exhibit B, in my former role as Roche's Chief Patent Counsel, I was involved in the budgeting of costs for patent litigation, including Hatch-Waxman litigation. I also have advised senior management in establishing budgets and estimating the timing and duration for these litigations. I also interfaced with outside litigation counsel in reviewing litigation counsel's invoices in connection with these litigations. In my opinion, the expectations of a reasonable and competent patent attorney involved with Hatch-Waxman litigations would be in line with my experience.

420. In my experience, the costs of litigating a patent infringement lawsuit are often categorized as falling into two bins: (1) pretrial work up through the close of expert discovery; and (2) work following the close of expert discovery. The latter typically includes:

(a) dispositive and *Daubert* motions and the preparation of the pretrial order;

(b) trial preparation and trial;

(c) post-trial briefing; and

(d) appellate work.

[162] FRX-AT-04248512 –FRX-AT-04248513.

421. At the time Mylan's counsel wrote to the District Court advising that the parties had reached an agreement-in-principle (*i.e.*, on March 16, 2010), the scheduled start of the trial (*i.e.*, April 5, 2010) was just three weeks away, and no dispositive or *Daubert* briefing was scheduled. Moreover, the pretrial order had been filed previously. *See* Pretrial Order at MNAT_0000001-011. As a result, any subsequent saved litigation costs would relate to above items (b) trial preparation and trial; (c) post-trial briefing; and (d) appellate work. In my experience, a reasonable and competent patent attorney in a Hatch-Waxman lawsuit would anticipate spending about $1,000,000 to $1,500,000 to prepare for and conduct a one-week trial. In addition, a reasonable and competent patent attorney in a Hatch-Waxman lawsuit would anticipate spending about $1,500,000 on post-trial briefing and appellate work. Thus, based on my experience, I would expect Forest/Merz, and Mylan's saved litigation costs resulting from the settlement were about $2,500,000 to $3,000,000.

422. AIPLA Survey. I have cross checked my above experience basis against AIPLA survey information. The AIPLA conducts yearly surveys and reports data pertaining to the "typical costs of litigation" for patent litigation in cases in which over $25 million was at risk. *See, e.g.*, *Report of the Economic Survey*, AIPLA, (2009) (**"2009 Survey"**), at 29; *see also Report of the Economic Survey*, AIPLA, (2011) ("**2011 Survey"**), at 35. The Namenda Litigation was a case in which over $25 million was at risk[163]. In 2009, the AIPLA reported that $3,731,000 was the average total cost of patent litigation through the end of discovery where greater than $25 million was at risk. 2009 Survey at I-129. The AIPLA also reported that $6,250,000 was the average total cost of patent litigation through the end of litigation, including appeal. *Id.* The AIPLA further reported that for the 75th percentile of litigations, litigation costs amount to $5,000,000 through the end of discovery. *Id.* The AIPLA reported that for the 75th percentile of litigations, litigation costs amount to $8,000,000 through the end of litigation, including appeal. *Id.*

423. In 2011, the AIPLA reported that the average cost of patent litigation was $3,553,000 through the end of discovery where greater than $25 million was at risk. 2011 Survey at I-154. The AIPLA reported that the average total cost of patent litigation through the end of litigation was $6,018,000, including appeal. *Id.* The AIPLA reported that for the 75th percentile of litigations, litigation costs amount to $5,000,000 through the end of discovery. *Id.* The AIPLA reported that for the 75th percentile of litigations, litigation costs amount to $7,500,000 through the end of litigation, including appeal. *Id.*

424. Both the 2009 and 2011 Surveys explained that cost includes "outside legal and paralegal services, local counsel, associates, paralegals, travel and living expenses, fees and costs

[163] According to Forest and Merz, Namenda's gross sales in Fiscal Year 2009 exceeded $1 billion. Pretrial Order, Exhibit 11, ¶ 13.

for court reporters, photocopies, courier services, exhibit preparation, analytical testing, expert witnesses, translators, surveys, jury advisors, and similar expenses." 2009 Survey at 29; 2011 Survey at 35. The surveys also specified that the "total cost" through the end of litigation is "inclusive of discovery, motions, pretrial, trial, post-trial, and appeal." 2009 Survey at App. B, 7 (question 40); 2011 Survey at App. B, 7 (question 42).

425. The following Table summarizes the patent litigation costs as reported in the AIPLA Report of the Economic Survey for 2009 and 2011 and described above.

Table - AIPLA Report of the Economic Survey for 2009 and 2011 Cases with over $25 Million at Risk

	2009 AIPLA Survey		2011 AIPLA Survey[164]	
Cost	**Average**	**75th Percentile**	**Average**	**75th Percentile**
End of Discovery	$3,731,000	$5,000,000	$3,553,000	$5,000,000
Total Cost All Inclusive	$6,250,000	$8,000,000	$6,018,000	$7,500,000
Percentage of Total Cost accrued by End of Discovery	59.7%	62.5%	59%	66.7%

426. Although the numbers vary slightly from 2009 to 2011 and from the average case to the 75th percentile case, AIPLA's survey shows that the cost of proceeding from the end of discovery through appeal varies from about $2,500,000 to $3,000,000 for this group of cases. This result appears to confirm generally my estimate based on my experience as chief patent counsel that Mylan and Forest/Merz saved $2,500,000 to $3,000,000.[165]

427. The Kirkland Estimate. Third, I understand that on March 23, 2009, Forest and Merz's counsel, Kirkland & Ellis LLP, provided Forest and Merz with an "estimate of Kirkland's currently anticipated total litigation costs per quarter from the start of second quarter

[164] For completeness, I note that in the AIPLA Surveys there are some unexplained reductions from 2009 to 2011. In my opinion, the differences (at most 6.25%, (*i.e.*, $8.0M - $7.5M)/$8.0M)) are not material to my calculations or opinions.

[165] However, for completeness and transparency, I note that the AIPLA survey numbers from the end of discovery through appeal include the cost of dispositive and *Daubert* briefing and the preparation of the pretrial order, whereas (for the reasons explained above) Forest/Merz, and Mylan did not save those costs by settling. In my experience, the cost of dispositive and *Daubert* briefing and the preparation of the pretrial order can be on the order of $500,000, thereby reducing the AIPLA numbers to about $2,000,000 to about $2,500,000, which is about $500,000 less than my above estimate based on my personal experience. However, this $500,000 difference can be reconciled. The AIPLA data included data from all patent litigations, not just Hatch-Waxman litigations. From my experience, Hatch-Waxman litigations generally constitute one of the more costly types of patent litigations. Accordingly, in my experience, $500,000 in increased costs for a Hatch-Waxman litigation over the costs found in the AIPLA data would not be out of line.

2009 through potential appeal" ("**Kirkland Estimate**"). The letter summarized the anticipated costs which have been tabulated below:

Table – Kirkland Estimate of Anticipated Litigation Cost for Forest and Merz

Quarter	Amount	Activity
Q2 '09	$1.5M	Fact Discovery
Q3 '09	$1.75M	Expert Discovery
Q4 '09	$1.5M	Trial Preparations
Q1 '10	$1.5M	Trial Preparations
Q2 '10	$2.5M	Trial and Post-trial Briefs
Q3 '10	$1.0M	Appeal Costs
Total	**$9.75M**	

428. In my opinion, the Kirkland Estimate supports the view that Forest/Merz saved about $3,500,000 through the settlement with Mylan, which corresponds to the sum of the contemplated costs in the second and third quarters of 2010. In my opinion, there would be no saved litigation costs attributable to the first quarter of 2010. First, at the time the parties notified the court of an agreement-in-principle to settle the Namenda Litigation on March 16, 2010, the first quarter of 2010 was already almost over and thus the costs attributable to that quarter were largely already sunk. *See* March 16, 2010 letter from Daniel V. Folt of Duane Morris to the Honorable Judge Gregory M. Sleet, ECF No. 479. Second, Mylan specifically requested that the "current April 5 trial date be preserved . . . ." *Id.* As a result and in my opinion, a reasonable and competent patent attorney would have continued preparation for the scheduled April 5, 2010 trial[166]. The remaining anticipated costs in the budget (*i.e.,* Q2 '10 and Q3 '10) are $3,500,000, and in my opinion correspond to costs that Forest/Merz saved by settling with Mylan.

429. The estimate of Forest/Mertz's saved litigation expenses based on the Kirkland Estimate (*i.e.*, $3,500,000) is somewhat higher than my estimate of $2,500,000 to $3,000,000. However, in my opinion, the Kirkland Estimate generally can be reconciled with my prior estimate. At the time of the Kirkland Estimate in March 2009, Forest and Merz were litigating against a substantial number of generic drug companies and Kirkland's estimate related to the cost of all of those litigations. For example, there would be costs associated with responding to each Generic Company's various motions, pretrial briefs, and communications between outside counsel. Based on my experience, I would estimate these additional costs at about $500,000 to $1,000,000. More specifically, the subject line of the Kirkland Estimate is "U.S. Namenda Enforcement Actions" and the text of the

[166] For completeness, I note that the complaint in the current JM Smith Corporation vs. Actavis PLC *et al.* matter states that Forest and Merz settled with Mylan "on or about July, 2010." Complaint at ¶ 113.

document reflects that it is "an estimate of Kirkland's currently anticipated total litigation costs per quarter from the start of second quarter 2009 through potential appeal of the above referenced actions." FRX-AT-04248512. Thus, the Kirkland Estimate in March 2009 likely anticipated the possibility for a multi-party trial, and complex post-trial and appellate briefing.

430. At the time of the settlement with Mylan, however, the sole defendant in the trial and any appeal was Mylan, and thus the 2009 Kirkland Estimate might have overstated the remaining litigation costs for Forest/Merz as of March 2010. In my opinion, that change in the Namenda Litigation between March 2009 and March 2010 – *i.e.*, the simplification of the Namenda Litigation via the settlement of a large number of generics – explains the difference between (1) the Kirkland Estimate; and (2) my experience and the AIPLA survey data.

431. In any event, I shall utilize the Kirkland Estimate in estimating the litigation cost savings of Forest/Merz from the settlement with Mylan. The Kirkland Estimate is specific to the Namenda Litigation, whereas my personal experience, as well as the AIPLA data, is derived from other cases. Therefore, I shall use the Kirkland Estimate as reflecting the highest reasonable estimate of saved litigation costs by Forest and Merz.

432. Based upon the foregoing, it is my opinion that the settlement of the Namenda Litigation between Forest/Merz on the one hand and Mylan on the other hand generated the following saved litigation costs: (1) for Forest/Merz, $3,500,000; and (2) for Mylan, $2,500,000 to $3,000,000.

XV. OTHER

A. Materials Considered and Relied Upon

433. Pursuant to Fed. R. Civ. P. 26(a)(2)(B), in preparing this Report I have reviewed and relied upon, to a greater or lesser degree, the documents set forth in Exhibit O and/or cited in this report. I reserve the right to rely upon any additional documents, materials, or information that may be provided to me, that may be relied upon by any opposing expert, or that is developed at or prior to trial.

B. Prior Testimony

434. I have never testified at trial. I have been deposed as a fact or 30(b)(6) witness pursuant to my role at Roche thrice in the last five years:

- *Hoffmann-La Roche Inc. v. Mylan Inc. and Mylan Pharms., Inc.*, Civil Action No. 09-1692 (ES)(CLW) (D.N.J. and *Hoffmann-La Roche Inc. v. Roxane Labs., Inc., et al.*, Civil Action No. 09-6335 (ES)(CLW) (D.N.J.);

- *Hoffmann-La Roche Inc. et al. v. Apotex, Inc. et al.*, Civ. No. 07-4417 (SRC)(MAS) (D.N.J.) (consolidated for all purposes with Civ. Nos. 08-3065, 08-4053, and 10-6241); *Hoffmann-La Roche, Inc. et al. v. Cobalt Pharms. Inc.* et al., Civ. No. 07-4539 (SRC)(MAS) (D.N.J.) (consolidated for all purposes with Civ. Nos. 07-4550, 08-4054, and 10-6206); *Hoffmann-La Roche Inc. et al, v. Dr. Reddy's Labs*, Civ. Nos. 07-4516 (SRC) (MAS) (D.N.J) (consolidated for all purposes with Civ. Nos. 08-3607, 08-4055, and 10-5623); *Hoffmann-La Roche, Inc. et al. v. Orchid Chems. & Pharms. Ltd. et al.*, Civ. No. 07-4582 (SRC)(MAS) (D.N.J.) (consolidated for all purposes with Civ. Nos. 08-4051 and 10-4050); and *Hoffmann-La Roche Inc. et al. v. Genpharm Inc. et al.*, Civ. No. 07-4661 (SRC)(MAS) (D.N.J.) (consolidated for all purposes with Civ. Nos. 08-4052 and 11-0579); and

- *Immunex Corporation et.al. v, Sandoz, Inc. et al.*, Civil Action No. 16 CV 1118 (CCC)(JCB) (D.N.J).

435. I also have been deposed pursuant to my role as an Expert Witness twice in the last five years:

- *Henryk Olesky v. General Electric Corporation et.al.*, Civil Action No. 1:06-CV-01245 (VMK) (N.D. Ill.)

- *Children's Medical Center Corporation and CR REV Holdings LLC, v. Celgene Corporation*, Civil Action No. 13-CV-11573 (MLW)(JGD) (D. Mass.)

C. Compensation

436. My employer, Gibbons P.C., is being compensated for the time I have devoted to working on this Report at a rate of $700 per hour for the time I spend in this case. Gibbons P.C. expects to be compensated at the same rate for my time spent testifying by deposition or at trial in this matter. I am a salaried employee of Gibbons P.C. and am not receiving any additional compensation for working on this litigation other than my usual salary. The compensation for the time I spend in this case in no way depends on the outcome of this litigation or on my conclusions or opinions in this Report.

Date: September 15, 2017

George W. Johnston, Esq.

Exhibit Index

Exhibit	Description
A	George Johnson CV
B	George Johnston Qualifications and Experience
C	Patenting Process and Procedures – Description
D	Patenting Process – Flow Chart
E	Copy of Forest's PTE Worksheet
F	U.S. Patent No. 5,061,703 – Originally Issued Claims
G	U.S. Patent No. 5,061,703 – Claims After Reexamination
H	PTE Application Chronology
I	Canadian and German Patent Claims
J	Defenses Raised in Paragraph IV Notice Letters
K	*Markman* Summary Chart
L	Namenda Litigation Timeline
M	Legal Understanding
N	Due Diligence Timeline
O	Materials Considered

EXHIBIT A

George W. Johnston
CURRICULUM VITAE

100 Poplar Drive
Cedar Knolls, NJ 07927
www.linkedin.com/in/gwjohnston/

(201) 341-7035 (cell)
gjohnston@gibbonslaw.com

Intellectual Property and Licensing professional with extensive pharmaceutical experience as in-house Chief Patent Counsel and at a major patent law firm. Specific experiences include:

Patent Preparation and Prosecution
Hatch Waxman Act
Pediatric Exclusivity Rights
Global Intellectual Property Counseling
Patent Litigation
Orphan Drug Protection
Patent Term Extensions and Adjustments
Licensing

Professional Experience

Gibbons P.C. – Newark, NJ

Counsel (10/2013 – present)
Preparation, prosecution, licensing, and litigation of patents, as well as counseling on intellectual property matters, with a particular focus on the pharmaceutical and biotechnology industries. Expert Witnessing.

Hoffmann-La Roche Inc., Nutley, NJ

Vice President and Chief Patent Counsel (1996 – 2013)
Led IP team of 15 professionals responsible for creating and implementing strategic frameworks that strengthened Roche's intellectual property during the entire pharmaceutical product life cycle.
Oversaw preparation, prosecution, IP due diligence analyses, and counseling on intellectual property matters.
Directed the development of strategies and supervised outside counsel involving major offensive and defensive patent litigations, including Hatch Waxman Paragraph IV suits.

Vice President, Licensing (1996 – 2003)
Headed Roche's US Licensing group (including transactional attorneys and business development representatives) and oversaw the negotiation and preparation of US strategic alliances (e.g., co-promotion agreements, research collaborations, and in- and out-licenses).

Assistant Secretary (1988 – 1996)
Interfaced regularly with Senior Management on general corporate matters, Executive Committee and Board of Directors meetings and resolutions.

Other Roche Positions - Ascended through the patent ranks from Patent Counsel to Associate Chief Patent Counsel and held senior officer positions at various Roche affiliates.

George W. Johnston
CURRICULUM VITAE

Education

Rutgers University School of Law, Newark, NJ
Juris Doctor
Editor, Rutgers Computer and Technology Law Journal

Stevens Institute of Technology, Hoboken, NJ
Bachelor of Engineering with High Honor (concentration Chem. Eng.)
Tau Beta Pi (National Engineering Honor Society)
AIChE Chapter President

Admission

Registered Attorney - U.S. Patent and Trademark Office
New York Bar
New Jersey Bar
Court of Appeals of the Federal Circuit
U.S. District Courts: DNJ, SDNY, and EDNY

Publications

- ***Federal Appeals Court Directs FDA to Treat Reissue Patents as Separate and Distinct When Determining Eligibility for Pre-MMA 180-Day Exclusivity***
  Wendy R. Stein and George W. Johnston
  Gibbons Blog
  January 13, 2015

- ***Inter Partes Review: Generic Pharma Has Found a Powerful Patent-Busting Weapon***
  David E. De Lorenzi and George W. Johnston
  New Jersey Law Journal IP Supplement
  September 15, 2014

- ***It Ain't that Obvious to Try***
  George W. Johnston and Andrew P. MacArthur
  Gibbons Blog
  May 9, 2014

- ***Potential For Harm: Indemnity Agreements and Willfulness Determinations***
  George W. Johnston and James Kang
  Gibbons Blog
  March 4, 2014

- ***Big Pharma Mutating from Small Molecules into Biotech Drugs***
  George W. Johnston
  Gibbons Blog
  November 25, 2013

EXHIBIT B

Qualifications and Experience
George W. Johnston

1. In 1972, I received my Bachelor of Engineering degree with high honor (chemical engineering concentration) from Stevens Institute of Technology, Hoboken New Jersey, and, in 1975, I received my J.D. from Rutgers University School of Law, Newark, New Jersey. At Rutgers, I served for two years on what is now known as the Rutgers Computer and Technology Law Journal, including one year as an editor.

2. I have been admitted to practice law in the State of New Jersey since 1975, the State of New York since 1976, the Federal District Court for the District of New Jersey since 1975, the Federal District Court for the Southern District of New York since 1976, the Federal District Court for the Eastern District of New York since 1976, and the Court of Appeals for the Federal Circuit since 1982. I have also been registered to practice before the USPTO since 1976.

3. After graduating from law school, I began my career in private practice as an associate at Pennie & Edmonds in New York. My responsibilities involved working on patent litigations and regulatory matters as well as prosecuting patents before the USPTO. My work involved various technologies, including the mechanical and chemical arts.

4. In 1977, I joined the in-house legal department of Roche. I was a Patent Attorney and my duties included patent application preparation, filing and prosecution, including pharmaceutical inventions ("**Patenting**"). After I was appointed Patent Counsel in 1980, my duties included Patenting and patent litigation. In 1985, I was appointed Senior Patent Counsel. My duties included Patenting, patent litigation, and assisting in the licensing of technologies.

5. From 1988 to 1996, I also served as Assistant Corporate Secretary for Roche. My duties included interfacing with Roche Senior Management on general corporate matters, attending Executive Committee and Board of Directors meetings, and overseeing the preparation and execution of minutes and corporate resolutions.

6. In 1989, I was appointed Assistant Chief Patent Counsel at Roche. My duties included overseeing Patenting by other members of the Roche Patent Department, patent litigation, and licensing, including assisting in preparing and negotiating agreements. I also supervised patent attorneys and assisted with departmental administration. In 1991, I was appointed Associate Chief Patent Counsel. My duties included overseeing Patenting by other members of the Roche Patent Department, patent litigation, leading preparation and

negotiation of agreements, managing a group of Roche patent attorneys, and departmental administration. I also represented the Roche Patent Department on cross functional teams within Roche involved with drug development and United States Food and Drug Administration approval to market.

7. From 1995 to 2011, I also served as Assistant Corporate Secretary of Roche Laboratories, Inc., a wholly-owned subsidiary of Roche. My duties included interfacing with Roche Laboratories Senior Management on general corporate matters and overseeing the preparation and execution of corporate resolutions.

8. From 1996 to 2003, I also served as the Vice President of Licensing at Roche. My duties included overseeing, coordinating, and directing Roche's in-licensing and out-licensing activities involving Roche-originated and third-party products, and representing the Roche Licensing Department on cross functional teams within Roche regarding licensing and acquisition of drug candidates.

9. From 1996 to 2013, I also served as Chief Patent Counsel and Vice President of Roche. My duties as Chief Patent Counsel included managing the Roche patent department, including responsibility for Roche's U.S. patent portfolio. More particularly, my duties and responsibilities as Roche's Chief Patent Counsel included: (a) managing all U.S. Roche patent litigations; (b) overseeing and supervising the preparation and prosecution of all U.S. Roche patent applications; (c) counseling Roche business units on intellectual property matters; (d) overseeing the legal strategies and negotiations of Roche's licensing transactions with third parties; and (e) obtaining and reviewing freedom to operate opinions related to all Roche U.S. patent matters.

10. Among other things, the business units of Roche relied on my department to obtain intellectual property protection for early research drug candidates, clinical candidates, and approved products. As part of overseeing Patenting, I also made the final decision on prosecution and patent litigation issues under U.S. patent law.

11. From 1999 to 2003, I also served as Vice President of HLR Technology Corporation, an intellectual property holding corporation wholly owned by Roche. As Vice President of HLR Technology Corporation, I was responsible for overseeing, coordinating, and directing its patent portfolio.

12. From about 1986 to 1988, I was the inaugural Chair of the Patent Law Committee for the Industrial Biotechnology Association (now the Biotechnology Industry Organization, known as "**BIO**"). From about 2005 to 2013, I was a member of the Board of Directors

of the Intellectual Property Owners Association ("**IPO**"), a leading advocate for protecting Intellectual Property rights.

13. Since 2007, I also have served on the Advisory Board of the Gibbons Institute of Law, Science, and Technology at Seton Hall Law School, which provides a forum for lawyers, judges, scientists, and government officials to discuss the legal, political, and social problems that arise as scientific and technological changes challenge our existing laws and legal institutions. Since May 2013, I have served on the Board of Trustees for the New Jersey Inventors Hall of Fame, which honors New Jersey inventors and promotes their role in technology, improving society, and changing lives.

14. Since 2005, I have been a member of the American Conference Institute's ("**ACI**") Advisory Board on the Hatch-Waxman Act, and for over a decade, I co-chaired ACI's annual Maximizing Pharmaceutical Patent Life Cycles Conference. I now co-chair ACI's annual Life Sciences Patents Conference.

15. Over my career, I have also made presentations on various aspects of patent law at Roche and its affiliates in the United States and abroad and at external organizations, such as the New York Intellectual Property Law Association, the New Jersey Intellectual Property Law Association, ACI (Hatch Waxman Master Paragraph IV Conference, Maximizing Biopharmaceutical Patent Life Cycles Conference), BIO, and the Pharmaceutical Educational Research Institute. In addition, I have lectured on various aspects of patent law at Seton Hall Law School, Columbia University (Graduate Program in Biosciences), Weill Cornell Medical School (*Bench to Bedside* Entrepreneurs Initiative), Rutgers University School of Law, and Rutgers University Business School (MBA Program in Pharmaceutical Management and Pharmaceutical Executive Education Program).

EXHIBIT C

TABLE OF CONTENTS

Page

PATENTING PROCESS AND PROCEDURES

I. Patent Procedures

A. Patent Prosecution Proceedings

1. A U.S. patent provides the patent holder with the right to seek to exclude others from making, using, selling, or importing the invention claimed in the patent for the period during which the patent is in force. 35 U.S.C. § 154.

2. In order to obtain a U.S. patent, an inventor must file an application with the USPTO. The application comprises a specification with claims, as prescribed by Title 35 of the United States Code. The specification contains a written description of what the applicant believes to be his or her invention. 35 U.S.C. § 112. It also must be written in a clear and concise manner to enable others who are knowledgeable about the technology (*i.e.*, skilled in the art) to make and use the invention. *Id.*

3. The patent specification must conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his or her invention. In other words, the claim language must be "definite" to comply under 35 U.S.C. § 112. The claimed invention also must be directed to patentable subject matter (35 U.S.C. § 101), be novel (35 U.S.C. § 102), and be nonobvious over the prior art (35 U.S.C. § 103).

4. Once an application is filed, the USPTO reviews the application to determine whether it satisfies the requirements set forth in the patent statute mentioned above. M.P.E.P. § 702. This review is an *ex parte* process in which third parties typically do not participate. For a graphic overview of this process, please see the flow chart attached as **Exhibit D.**

5. As part of the USPTO review process, a patent examiner is assigned to read the specification and claims. Upon review, an examiner may find that the claims of the patent application contain more than one invention. As a result, the examiner may divide the patent claims into groups of separate inventions. The patent applicant then is asked by the examiner to choose one of these groups of claims for further prosecution in the present application. The remaining groups of claims can be prosecuted in subsequent applications filed by the applicant. These subsequent applications are called "Divisionals" or "Divisional Applications." M.P.E.P. § 201.06

6. After the applicant selects a single invention (*i.e.*, a specific group of claims), the examiner conducts a prior art search looking for prior art references (*i.e.*, publications and

patents) that might contain subject matter that predates the claimed invention being examined. With the results of the prior art search, including any references provided by the applicant, the examiner analyzes the patent application in conjunction with the identified prior art references to determine whether the claims define a useful, novel, nonobvious, and enabled invention that has been described in the specification. M.P.E.P. § 706.

7. "More than one claim may be presented for examination provided they differ substantially from each other and are not unduly multiplied." M.P.E.P. § 608.01(i). A claim may be presented in "dependent" form that refers back to and further limits another claim or claims in the same application. *Id.* Claims presented in dependent form are "construed to include all the limitations of the claim incorporated by reference into the dependent claim." *Id.*

8. "The goal of examination is for the examiner to clearly articulate any rejection early in the prosecution process so that the applicant has the opportunity to provide evidence of patentability and otherwise reply completely at the earliest opportunity." M.P.E.P. § 706.

9. If the examiner determines that the specification or claims do not satisfy the above requirements, the examiner may send to the patent applicant (*i.e.*, "issue") an Office Action, including a non-final or final rejection. An applicant may respond to the Office Action with or without amending the specification or claims. Upon receiving an applicant's response to an Office Action, the examiner then reviews the applicant's arguments and evidence responsive to any rejection. *Id.*

10. Once the examiner is satisfied that the claims being examined meet the statutory requirements, the examiner may issue a Notice of Allowability indicating that the application has been placed in condition for allowance. Thereafter, the USPTO sends a Notice of Allowance to the applicant indicating when a fee must be paid to allow the application to issue as a patent. M.P.E.P. §§ 1302, 1303.

B. *Ex Parte* Re-Examination Proceedings

11. Anyone, including a patent owner, may request that the USPTO reconsider (*i.e.*, reexamine) whether a claim in an issued U.S. patent meets certain statutory requirements for patentability. M.P.E.P. § 2203. The requestor may only submit prior art with a request and "must set forth the pertinency and manner of applying the cited prior art to every claim for which reexamination is requested." 35 U.S.C. § 302. The prior art submitted must consist of patents and printed publications which the requestor "believes to have a

bearing on the patentability" of a claim of the patent. 35 U.S.C. § 301. The request can be filed at any time during the term of a patent. M.P.E.P. § 2204.

12. Questions relating to grounds of rejection other than those based on prior art patents or printed publications may *not* be included in a request for reexamination and will not be considered by the USPTO, if included. Examples of such questions that will not be considered are public use, on sale, and conduct by parties. M.P.E.P. § 2216.

13. The requester must establish that the submitted prior art establishes a "substantial new question of patentability." The requester must demonstrate that a patent or printed publication presents a "new, non-cumulative technological teaching that was not previously considered and discussed on the record during the prosecution of the application that resulted in the patent for which reexamination is requested, and during the prosecution of any other prior proceeding involving the patent for which reexamination is requested." *Id.*

14. "The substantial new question of patentability may be based on art previously considered by the Office if the reference is presented in a new light or a different way that escaped review during earlier examination." *Id.* Should the USPTO be convinced that a substantial new question of patentability exists, the USPTO will grant the request for reexamination and order reexamination of the patent. M.P.E.P. § 2242.

15. The resulting *ex parte* reexamination proceedings are generally similar to the regular examination process in patent applications. As the name suggests, *ex parte* reexamination proceedings generally involve only the patent owner and the USPTO. M.P.E.P. § 2212.

16. In an *ex parte* reexamination proceeding, the patent owner may propose any amendment to the patent and a new claim to distinguish the invention as claimed from the prior art cited. However, no proposed amended or new claim enlarging the scope of a claim of the patent is permitted in a reexamination proceeding. 35 U.S.C. § 305; M.P.E.P. § 2209.

17. "When the prosecution of a reexamination proceeding is terminated, a reexamination certificate is issued which indicates the status of all claims following the reexamination." M.P.E.P. § 2209.

C. Issued Claims

18. The scope protection afforded to a patent holder by a U.S. patent is defined by the issued claims of the patent – the "patented invention." The scope of the claims must be clear so the public is informed of the boundaries of what constitutes infringement of the patent.

The claims also are intended "to provide a clear measure of what applicants regards as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention." M.P.E.P. § 2173.

19. Patent infringement constitutes the acts of making, using, selling, offering for sale, or importing a patented product or methods that fall within the scope of the claims of a patent. Infringement is measured against the "patented invention," that is, the language of the issued claims. 35 U.S.C. § 271.

D. Patent Term

20. The term of a patent is the period during which the patent is in force. All patents that were in force on June 8, 1995, or that issued on an application that was filed before June 8, 1995, have a term that is the greater of (i) twenty (20) years from the date on which the application for the patent was filed in the United States or, if the application contains a specific reference to an earlier filed application or applications, twenty (20) years from the filing date of the earliest of such application(s) or (ii) seventeen (17) years from the patent grant. For applications filed on or after June 8, 1995, the term of a patent is the twenty-year term as described above. M.P.E.P. § 2701.

21. The term of a patent may be eligible for adjustment on account of prosecution delays within the USPTO under 35 U.S.C. § 154. M.P.E.P. § 2710.

22. The term of a patent also may be eligible for extension (*i.e.*, restoration) under 35 U.S.C. § 156 based on premarket regulatory review periods, such when those occurred when obtaining FDA approval to market a pharmaceutical product. The patent term extension that may be available under 35 U.S.C. § 156 for premarket regulatory review is separate from and is added onto any adjustment that may be available under 35 U.S.C. § 154. M.P.E.P. § 2701.

II. Pharmaceutical Patents and the Hatch-Waxman Act

A. Patent Term Extension

23. The Hatch-Waxman Act restored to the term of some pharmaceutical patents part of the time lost while awaiting FDA approval to commercially market a drug product that is covered by a patent. M.P.E.P. § 2750. A maximum of 5 years can be restored to a pharmaceutical patent term. Moreover, a "14-year cap" is also imposed on any extension, as will be explained further in this report. M.P.E.P. § 2758.

24. To extend a patent term, the patent owner or its agent must submit an application for the extension of the term of the patent which complies with the criteria of 35 U.S.C. § 156(a) and (d). A formal application for the extension of a patent term must include 15 items according to 37 C.F.R. § 1.740. The applicant must, *inter alia*,

- show that the patent has not expired;
- establish that the patent has not previously been extended;
- provide details about the patent and the activities undertaken to secure FDA approval;
- provide relevant dates and information to enable the Secretary of Health and Human Services ("**HHS Secretary**") to determine the applicable regulatory review period for the drug;
- establish that the product was subject to a regulatory review period before its commercial marketing or use;
- show that the product either represents the first permitted commercial marketing or use of the product after such regulatory review period;
- acknowledge its duty of candor and good faith toward the USPTO and the HHS Secretary to disclose all information which is material to the determination of entitlement to the extension sought ("**duty of disclosure**"); and
- submit the application for patent term extension to the USPTO within 60 days of FDA first approval of the commercial marketing application.

37 C.F.R. § 1.740; M.P.E.P. §§ 2751, 2752.

25. The USPTO initially determines whether the application formally meets the above criteria and whether the patent is eligible for extension. The USPTO then notifies the HHS Secretary of the submission of those applications for extension of a patent term which comply with the above requirements. The HHS Secretary then determines the length of the applicable "regulatory review period" and notifies the USPTO of its determination. M.P.E.P. § 2752.

26. The "regulatory review period" comprises two parts: a **testing phase** and an **approval phase**. The testing phase for a human drug product is the period between the effective date of an investigational product exemption (Investigational New Drug Application or "**IND**") and the initial submission of the marketing application (New Drug Application or "**NDA**"). The approval phase is the period between the submission and approval of the

NDA. 35 U.S.C. § 156(g)(1). The determination of the length of the "regulatory review period" is solely the responsibility of the HHS Secretary. M.P.E.P. § 2757.

27. For the HHS Secretary to establish the regulatory review period, the Applicant must provide in its Patent Term Extension ("**PTE**") Application:

- the effective date of the IND;
- the date on which a NDA was initially submitted; and
- the date on which the NDA was approved.

37 C.F.R. § 1.740.

28. The applicant also provides in its PTE Application the number of days during which the applicant did act not act with "due diligence" within each phase of the regulatory review period. 35 U.S.C. § 156(c); 37 C.F.R. § 1.775. Attached as Exhibit E is a copy of the USPTO worksheet Calculation of Length for Patent Term Extension for a Human Drug Product" used by Forest for the '703 patent.

29. Once the HHS Secretary determines the regulatory review period, the HHS Secretary publishes the information in the Federal Register including: (1) the total length of the regulatory review period and the relevant dates on which the determination is based; (2) a separation of the regulatory review period into the testing phase and the approval phase; and (3) a set date, 180 days after publication of the notice, as a deadline for a third party to file comments concerning any of the information set forth in the Notice as to whether the marketing applicant has acted with "due diligence" during the regulatory review period. M.P.E.P. § 2757.

30. The term "due diligence" in the context of a patent term extension is defined as "that degree of attention, continuous directed effort, and timeliness as may reasonably be expected from, and are ordinarily exercised by, a person during a regulatory review period." 35 U.S.C. § 156(d)(3).

31. If no comments are filed during the above 180-day period, the HHS Secretary notifies the USPTO that the period for filing comments has expired and that the HHS Secretary considers its determination of the regulatory review period for the product to be final. M.P.E.P. § 2757.

32. Based upon the information contained in the PTE Application and the regulatory review period as determined by the HHS Secretary, the USPTO calculates the length of extension for which the patent is eligible as follows:

- First, each phase of the regulatory review period is reduced by any time that the applicant did not act with due diligence during that phase. The reduction in time would occur after an FDA finding that the applicant did not act with due diligence.

- Second, after any such reduction, one-half of the time remaining in the testing phase would be added to the time remaining in the approval phase to comprise the total period eligible for extension.

- Third, the period of extension cannot exceed five years.

- Fourth, all of the eligible period is counted unless a total remaining patent term from the date of approval of a marketing application would exceed fourteen years. In other words, the total patent life for the product with the patent extension cannot exceed 14 years from the product's approval date – *i.e.*, 14 years of potential marketing time. For example, if an approved drug product which otherwise is eligible for the maximum of five years of extension had ten years of original patent term left at the end of its regulatory review period, then only four of the five years could be counted towards extension.

M.P.E.P. § 2758; 37 C.F.R. § 1.775.

33. The USPTO is responsible for determining the period of extension and issuing a Certificate of Extension. M.P.E.P. §§ 2758, 2759.

34. The Director of the USPTO is charged with deciding whether the patent is entitled to a term of extension. *See Pfizer, Inc. v. Ranbaxy Labs., Ltd.*, 457 F.3d 1284, 1290 (Fed. Cir. 2006).

B. The Orange Book

35. The Hatch-Waxman Act requires that a brand company provide to the FDA certain patent information on products for which the brand company has submitted an NDA for FDA approval to market those products. The FDA has taken the position that information on the following types of patents need to be provided under statutory provisions: drug substance patents that claim the active ingredient(s); drug product patents that claim formulations or compositions; and method of treatment patents that claim FDA-approved indications or methods of using the product. 21 C.F.R. § 314.53.

36. In particular, NDA holders are obligated to identify for the FDA "each patent that claims the drug or a method of using the drug that is the subject of the NDA or amendment or supplement to it and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the

manufacture, use, or sale of the drug product." 21 C.F.R. § 314.53(b)(1). The FDA publishes this information in the Orange Book. For patents that claim a method of use, the NDA applicant also must identify each pending or approved method of use and related patent claim. 21 C.F.R. § 314.53.

C. Hatch-Waxman Litigation

37. A generic manufacturer must address any patents listed in the Orange Book for a particular product when submitting a request for approval of an Abbreviated New Drug Application ("**ANDA**") seeking to market a generic equivalent product. For each Orange Book-listed patent, the ANDA applicant must certify to the FDA that the patent has expired (Paragraph II submission), that the applicant will not market its generic equivalent product until after the patent has expired (Paragraph III submission), or that the patent is invalid and/or will not be infringed by marketing the generic equivalent product ("**Paragraph IV submission**"). 21 U.S.C. § 355.

38. Should an ANDA applicant choose to submit a Paragraph IV submission to the FDA, it must also notify the patent and NDA owner(s), who can then bring suit against the ANDA applicant for patent infringement. Once an infringement suit has been filed, an automatic stay is triggered, during which time the FDA is prohibited from approving the ANDA. 21 U.S.C. § 355.

39. Should a court determine that the generic equivalent product infringes the listed patent(s), it issues an order prohibiting the FDA from approving the ANDA until the expiration of the specific patent(s). Should a court determine that the generic equivalent product does not infringe any of the listed patent(s), or that all of the listed patent(s) are invalid (or a combination of non-infringement and invalidity), the FDA is no longer prohibited from approving the ANDA. Once the FDA approves the ANDA, an ANDA applicant can begin selling its generic equivalent product. 21 U.S.C. § 355.

EXHIBIT D

Patenting Process

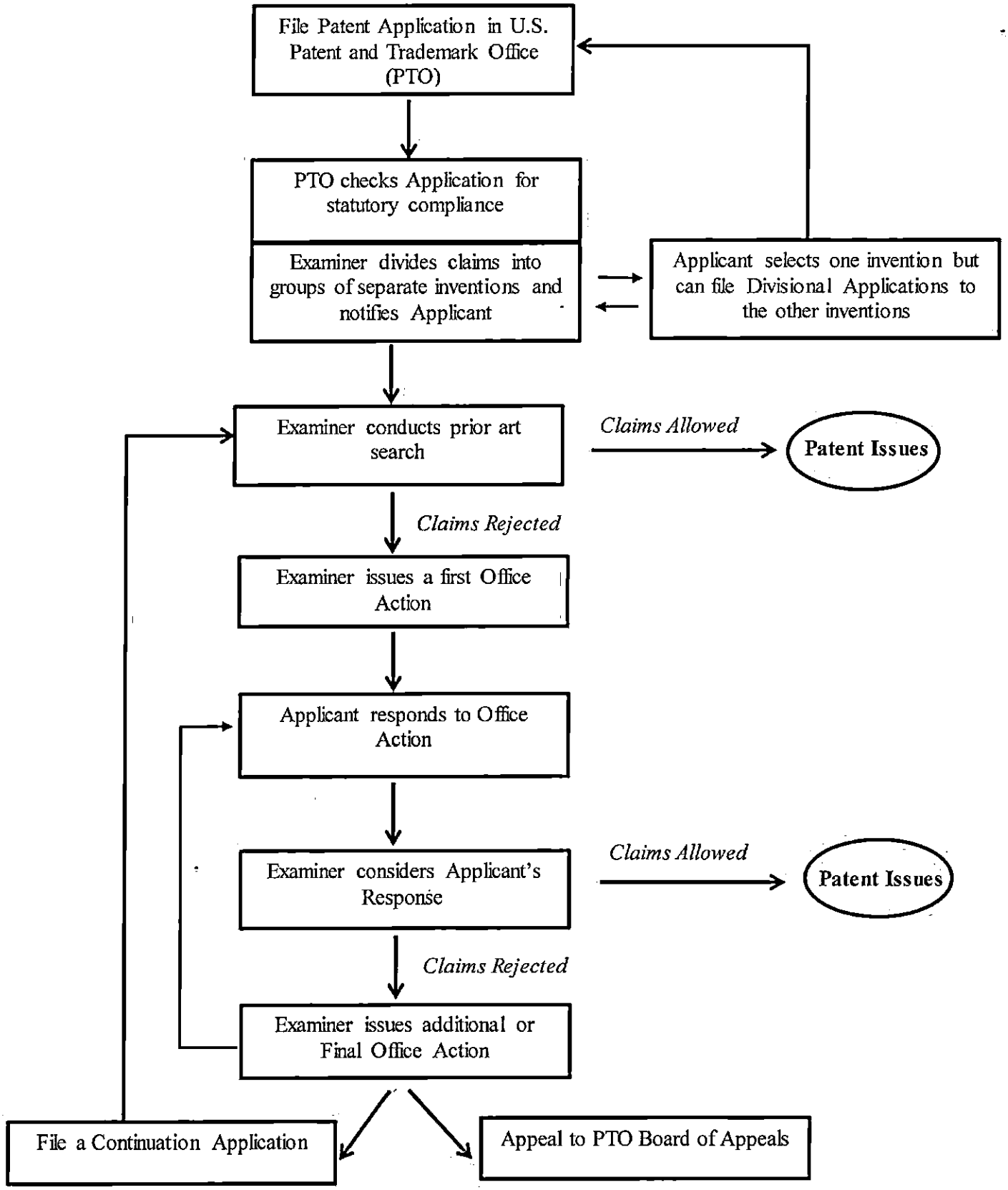


EXHIBIT E

Statement as to the Length of the Extension Claimed

In Accordance with 37 C.F.R. 1.775

The term of the '703 patent should be extended by 1250 days. The extension was determined according to 37 C.F.R. § 1.775 and the PTO worksheet "Calculation of Length for Patent Term Extension for a Human Drug Product" as follows:

(1)	1897	The number of days in: the period beginning on the effective date of the IND (October 9, 1997) and ending on the date the NDA was initially submitted (December 19, 2002). This is the "testing phase" as defined in 37 C.F.R. § 1.775(c)(1).

(2)	301	The number of days in the period beginning on the date the NDA was initially submitted (December 19, 2002) and ending on the date of NDA approval (October 16, 2003). This is the "approval phase" as defined in 37 C.F.R. § 1.775(c)(2).
(3)	2198	The sum of (1) and (2). This is the regulatory review period as define in 37 C.F.R. § 1.775(c).
(4)	0	The number of days in the approval phase (2) which were on and before issuance of the '703 patent. 37 C.F.R. § 1.775(d)(1)(i).
(5)	0	The number of days in the approval phase (2) during which the Applicant did not act with due dilligence. 37 C.F.R. § 1.775(d)(1)(ii).
(6)	0	The sum of (4) and (5).
(7)	2198	The difference between the regulatory review period (3) and (6). 37 C.F.R. § 1.775(d)(1)(ii).
(8)	0	The number of days of the period of the testing phase (1) which occurred prior to the issuance of the '703 patent. 37 C.F.R. § 1.775(d)(1)(i).
(9)	0	The number of days of the period of the testing phase (1) during which the Applicant failed to act with due dilligence 37 C.F.R. § 1.775(d)(1)(ii).
(10)	0	The sum of (8) and (9).
(11)	2198	The difference between the regulatory review period (7) and (10).
(12)	1897	The number of days of the testing phase (1).
(13)	0	The number of days from (10).
(14)	1897	Subtract line (13) from line (12)
(15)	948	One half of (14) 37 C.F.R. § 1.775(d)(1)(iii)[1]
(16)	1250	Subtract line (15) from line (11)
(17)	April 11, 2010	The original expiration date of the '703 patent.
(18)	Sept. 12, 2013	The expiration date of the '703 patent if the original expiration date is extended by the number of days in line (16). 37 C.F.R. § 1.775(d)(2)
(19)	Oct. 16, 2003	The date of approval of the application under § 505(b) of the FFDCA.

[1] 37 C.F.R. § 1.775(d)(1) provides that for purposes of subtraction, half days are ignored.

(20)	14 years	The limitation of 37 C.F.R. § 1.775(d)(3).
(21)	Oct. 16, 2017	The number of years in (20) plus the date on (19). 37 C.F.R. § 1.775(d)(3).
(22)	Sept. 12, 2013	The earlier of line (18) or line (21)
(23)	April 11, 2010	The original expiration date of the '703 patent.
(24)	5 years	The applicable limitation of 37 C.F.R. § 1.775(d)(5)
(25)	April 11, 2015	The number of years on (24) plus the date on (23).
(26)	Sept. 12, 2013	The earlier of line (22) or line 25
(27)	April 11, 2010	The original expiration date of the '703 patent
(28)	1250	The number of days which is the difference between the date on line (27) and the date on line 26

(13) A statement that the Applicant acknowledges a duty to disclose to the Commission of Patents and Trademarks and to the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought for the '703 patent by this Request as required by 37 C.F.R. § 1.765.

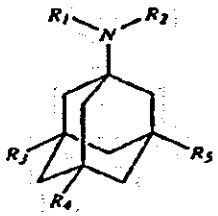
(14) Prescribed Fee:

A check in the amount of $1,120.00 required under 37 C.F.R. § 1.20(j) is enclosed with this Request. The Commissioner is authorized to charge any additional fees to Darby & Darby P.C., Deposit Account No. 04-0100.

EXHIBIT F

The originally issued claims of the '703 patent are as follows:

Claim 1: A method for the prevention or treatment of cerebral ischemia comprising the step of administering, to a patient in need thereof, an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group,

or a pharmaceutically-acceptable salt thereof.

Claim 2: A method according to claim **1**, wherein R_1, R_2 and R_5 are hydrogen.

Claim 3: A method according to claim **2**, wherein R_1, R_2 and R_5 are hydrogen, and R_3 and R_4 are methyl.

Claim 4: A method according to claim **2**, wherein R_1, R_2 and R_5 are hydrogen, and R_3 and R_4 are ethyl.

Claim 5: A method according to claim **1**, wherein R_1, R_2, R_4 and R_5 are hydrogen, and R_3 is ethyl, isopropyl, or cyclohexyl.

Claim 6: A method according to claim **1**, wherein R_2 and R_5 are hydrogen.

Claim 7: A method according to claim **6**, wherein R_3 and R_4 are methyl, R_2 and R_5 are hydrogen and R_1 is methyl or ethyl.

Claim 8: A method according to claim **1**, wherein R_1 and R_2 are hydrogen.

Claim 9: A method according to claim **8**, wherein R_1 and R_2 are hydrogen, R_3 is ethyl, and R_5 and R_4 are methyl.

Claim 10: A method according to claim **1** for the treatment of Alzheimer's disease.

Claim 11: A method of claim **1**, wherein the adamantane derivative is administered in an effective cerebral ischemia-alleviating or preventative amount.

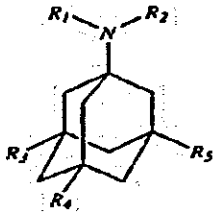
Claim 12: A method of claim **11**, wherein the adamantane derivative is administered in the form of a composition containing the same together with a pharmaceutically-acceptable carrier or diluent.

Claim 13: A method of claim **11**, wherein the adamantane derivative is administered in an amount effective to prevent degeneration and loss of nerve cells after ischemia.

EXHIBIT G

The reexamined claims of the '703 patent are as follows, in which the italicized words were added during reexamination:

Claim 1: A method for the prevention or treatment of cerebral ischemia comprising the step of *orally* administering, to a patient *diagnosed with Alzheimer's disease and* in need thereof, an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group, *and*

wherein

R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously,

or a pharmaceutically-acceptable salt thereof.

Claim 2: A method according to claim **1**, wherein R_1, R_2 and R_5 are hydrogen.

Claim 3: A method according to claim **2**, wherein R_1, R_2 and R_5 are hydrogen, and R_3 and R_4 are methyl.

Claim 4: A method according to claim **2**, wherein R_1, R_2 and R_5 are hydrogen, and R_3 and R_4 are ethyl.

Claim 5: A method according to claim **1**, wherein R_1, R_2, R_4 and R_5 are hydrogen, and R_3 is ethyl, isopropyl, or cyclohexyl.

Claim 6: A method according to claim **1**, wherein R_2 and R_5 are hydrogen.

Claim 7: A method according to claim **6**, wherein R_3 and R_4 are methyl, R_2 and R_5 are hydrogen and R_1 is methyl or ethyl.

Claim 8: A method according to claim **1**, wherein R_1 and R_2 are hydrogen.

Claim 9: A method according to claim **8**, wherein R_1 and R_2 are hydrogen, R_3 is ethyl, and R_5 and R_4 are methyl.

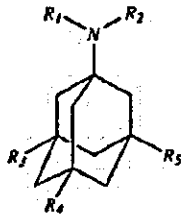
Claim 10: A method according to claim **1** for the treatment of Alzheimer's disease, *wherein said adamantane derivative is memantine and said effective amount is from about 0.01 mg to 100 mg/kg.*

Claim 11: A method of claim **1**, wherein the adamantane derivative is administered in an effective cerebral ischemia-alleviating or preventative amount.

Claim 12: A method of claim **11**, wherein the adamantane derivative is administered in the form of a composition containing the same together with a pharmaceutically-acceptable carrier or diluent.

Claim 13: A method of claim **11**, wherein the adamantane derivative is administered in an amount effective to prevent degeneration and loss of nerve cells after ischemia.

Claim 14: *A method for the treatment of cerebral ischemia comprising orally administering to a patient diagnosed with Alzheimer's disease and in need of such treatment an effective amount of an adamantane derivative of the general formula*



wherein

> *R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;*

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group; and

wherein

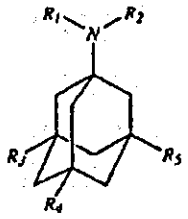
R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously,

or a pharmaceutically-acceptable salt thereof.

Claim 15: *The method of claim **14**, wherein said adamantane derivative is memantine.*

Claim 16: *The method of claim **14**, wherein said effective amount is from about 0.01 to 100 mg/kg.*

Claim 17: *A method for the treatment of an imbalance of neuronal stimulation after Alzheimer's disease, comprising orally administering to a patient diagnosed with Alzheimer's disease and in need of such treatment an effective amount of an adamantane derivative of the general formula*



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C1–C6 alkyl group; and

wherein

R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously,

or a pharmaceutically-acceptable salt thereof.

Claim 18: *The method of claim 17, wherein said adamantane derivative is memantine.*

Claim 19: *The method of claim 17, wherein said effective amount is from about 0.01 to 100 mg/kg.*

EXHIBIT H

Chronology - Patent Term Extension for '703 patent

Date	Description
07/10/89	IND for Namenda is filed with FDA and placed on clinical hold.
02/07/90	FDA releases the IND from clinical hold.
10/29/91	The '703 patent issues with thirteen claims directed to a method for the prevention or treatment of cerebral ischemia.
01/13/94	Merz requests that the IND be inactivated.
09/05/97	Merz requests the re-activation of the IND.
10/09/97	FDA "reactivates" the IND.
12/19/02	Namenda NDA is filed with the FDA.
10/16/03	FDA approves Namenda for commercial marketing and use.
12/09/03	Darby & Darby, P.C., ("Darby") files a Request for Patent Term Extension of the '703 patent on behalf of the patent owner, Merz, and requests an extension of the patent term by 1250 days (~3.4 years). The PTE Application states that the effective date of the IND is October 9, 1997 and that "0" days were to be subtracted for the number of days during the "testing phase . . . during which the Applicant failed to act with due diligence . . . ."
08/18/04	Darby files a request for *ex parte* reexamination of the '703 patent. The USPTO Director subsequently orders the reexamination.
09/21/06	USPTO requests a determination of the regulatory review period for Namenda from the FDA (*i.e.,* HHS Secretary). Darby is copied on the letter to the FDA.
11/07/06	USPTO issues an ex parte reexamination certificate, wherein original claims 1 and l0 of the'703 patent are amended and new claims 14-19 are added.
12/27/06	Darby files a Supplemental Request For Extension of Patent Term in the USPTO to indicate that the '703 patent had been reexamined and that a reexamination certificate had been issued.
01/26/07	FDA notifies the USPTO that Namenda had been subject to regulatory review and that its NDA had been approved on October 16, 2003. Darby is copied on the FDA letter.
02/28/07	USPTO notifies the FDA that the '703 patent is eligible for patent term extension. Darby is copied on the letter.
05/16/07	FDA makes a determination of the regulatory review period and concludes that the IND had an effective date of February 7, 1990, rather than October 9, 1997. Darby is copied on the letter.
06/05/07	A Federal Register notice is published regarding the FDA's determination with respect to the regulatory review period for Namenda requesting public comments or a petition challenging the determination.
07/13/07	Merz revokes the power of attorney to Darby and appointes Hueschen & Sage ("H&S") as new attorneys in the PTE proceeding.

Chronology - Patent Term Extension for '703 patent

02/21/08	FDA notifies the USPTO that having not received any comments or due diligence petitions, it regards its determination final. Darby is copied on the FDA letter.
11/11/08	Merz revokes the power of attorney to H&S and reappoints Darby as attorneys in the PTE proceeding.
11/13/08	Darby files a Second Supplemental Request for Patent Term Extension to indicate that new claims were issued directed to the treatment Alzheimer's disease.
11/21/08	Merz revokes the power of attorney to Darby and reappoints H&S as attorneys in the PTE proceeding.
03/03/09	USPTO issus a Notice of Final Determination (Notice) to H&S indicating that the period of extension is five years and gives the PTE Applicant one month to request reconsideration of the determination.
03/13/09	H&S notifies the USPTO that "the applicant [for the Request] respectfully accepts [the USPTO's] determination and waives its right to request reconsideration of the Notice of Final Determination. Acknowledgement of this waiver and issue of a certification of extension reflecting the five (5) year period of extension for US Patent No. 5,061,703 at the earliest possible time are all hereby respectfully solicited."
03/20/09	USPTO acknowledges receipt of H&S's waiver and issues a certificate of extension under 35 U.S.C. § 156 extending the term of the '703 patent for a period of five years.

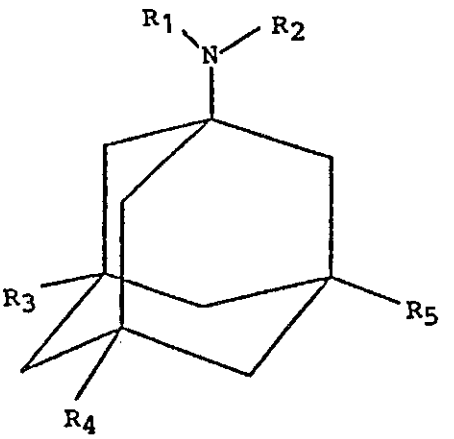
EXHIBIT I

Canadian Patent Claims

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

- 1 -

Use of an adamantane derivative of the general formula



(I)

wherein R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein R_5 is hydrogen or a straight or branched C_1 - C_6 alkyl group, or a pharmaceutically-acceptable salt thereof, for the prevention or treatment of cerebral ischemia.

- 25 -

Merz 16/bam

Use according to Claim 1, wherein R_1, R_2 and R_5 are hydrogen.

Use according to Claim 2, wherein R_1, R_2 and R_5 are hydrogen, and R_3 and R_4 are methyl.

Use according to Claim 2, wherein R_1, R_2 and R_5 are hydrogen, and R_3 and R_4 are ethyl.

Use according to Claim 1, wherein R_1, R_2, R_4 and R_5 are hydrogen, and R_3 is ethyl, isopropyl, or cyclohexyl.

Use according to Claim 1, wherein R_2 and R_5 are hydrogen.

Use according to Claim 6, wherein R_3 and R_4 are methyl, R_2 and R_5 are hydrogen and R_1 is methyl or ethyl.

Use according to Claim 1, wherein R_1 and R_2 are hydrogen.

Use according to Claim 8, wherein R_1 and R_2 are hydrogen, R_3 is ethyl, and R_5 and R_4 are methyl.

Use according to any of Claims 1-9 for the manufacture of a drug for the prevention or treatment of Alzheimer's disease.

Use according to Claim 1, wherein the adamantane derivative is used in an effective cerebral ischemia-alleviating or preventive amount.

Use according to Claim 11, wherein the adamantane derivative is used in an amount effective to prevent degeneration and loss of nerve cells after ischemia.

German Patent Claims

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Veröffentlichungsnummer: **0 392 059 B1**

(12) # EUROPÄISCHE PATENTSCHRIFT

(45) Veröffentlichungstag der Patentschrift: **15.09.93**

(51) Int. Cl.5: **A61K 31/13**, C07C 211/38

(21) Anmeldenummer: **89106657.3**

(22) Anmeldetag: **14.04.89**

Die Akte enthält technische Angaben, die nach dem Eingang der Anmeldung eingereicht wurden und die nicht in dieser Patentschrift enthalten sind.

(54) **Verwendung von Adamantan-Derivaten zur Prävention und Behandlung der cerebralen Ischämie.**

(43) Veröffentlichungstag der Anmeldung:
17.10.90 Patentblatt 90/42

(45) Bekanntmachung des Hinweises auf die Patenterteilung:
15.09.93 Patentblatt 93/37

(84) Benannte Vertragsstaaten:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) Entgegenhaltungen:
EP-A- 0 293 974
US-A- 3 450 761

RÖMPP CHEMIE LEXIKON, 9. Auflage, 1989, Seite 141&NUM;

W. Fleischhacker et al., PROG. NEURO-PSYCHPHARMACOL. & BIOL.-PSYCIATRY, 1986, Band 10, Nr. 1; Seiten 87-93&NUM;

J. PHARMACOL., Band 13, Nr. 1, 1982, Paris (FR); R. MARCY et al., Seiten 163-164&NUM;

JAPAN. J. PHARMACOL., Band 39, NR. 4, 1985, Kyoto (JP); Y.MIURA et al., Seiten 443-451&NUM;

(73) Patentinhaber: **Merz & Co. GmbH & Co.**
Eckenheimer Landstrasse 100-104
D-60318 Frankfurt(DE)

(72) Erfinder: **Bormann, Joachim, Dr.**
Stalburgstrasse 36
D-6000 Frankfurt am Main 1(DE)
Erfinder: **Gold, Markus R., Dr.**
Kranichstrasse 9
D-6085 Nauheim(DE)
Erfinder: **Schatton, Wolfgang, Dr.**
Dörnweg 11
D-6236 Eschborn(DE)

(74) Vertreter: **Beil, Hans Chr., Dr. et al**
BEIL, WOLFF & BEIL, Rechtsanwälte, Postfach 80 01 40
D-65901 Frankfurt (DE)

EP 0 392 059 B1

ARZNEIMITTELFORSCHUNG, Band 32, Nr. 10, 1982, Aulendorf (DE); F.O.MILTNER, Seiten 1268-1270, 1271-1273&NUM;

BRITISH MEDICAL JOURNAL, Band 3, Nr. 5874, 04 August 1973, London (GB); A.M.HAMOEN, Seiten 272-273&NUM;

NO SHINKEI GEKA, Band 12, Nr. 1, 1984, Tokyo (JP); H.KINOMOTA et al., Seiten 37-45&NUM;

DIALOG INFORMATION SERVICE, File 72, (Embase) Acc. Nr. 5254914 (Embase Nr. 83005619)&NUM;

THE MERCK MANUAL OF DIAGNOSIS & THERAPY, R. Berkow, MD Ed., 15.ausgabe, 1987, Merck & Co. Inc., Rahway, NJ (US); Seiten 1336-1340&NUM;

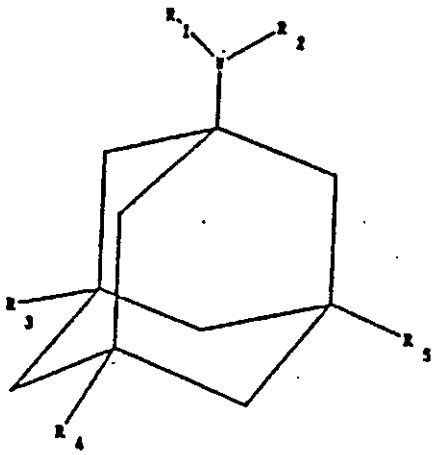
SBORNIK VISOKE SKOLY CHEMICKOTECHNOLOGICKE V PRAZE, Technologie Paliv, Band D 29, 1973, Praha (CS); J. BURKHARD et al., Seiten 91-97&NUM;

NAUNYN-SCHMIEDEBERGS ARCH. PHARMACOL., Band 332, Nr. 1, 1986, Berlin (DE); B.S.MELDRUM et al., Seiten 93-97&NUM;

POL. J. PHARMCOLI. PHARM., Band 35, Nr. 6, 1983, Warszawa (PL); E.CHOJNACKA-WOJCIK et al., Seiten 511-515&NUM;

Beschreibung

Die vorliegende Erfindung betrifft die Verwendung von Adamantanderivaten der allgemeinen Formel



(I)

worin R_1 und R_2 gleich oder verschieden sind und Wasserstoff oder geradkettige oder verzweigte Alkylgruppen mit 1 bis 6 C-Atomen bedeuten oder zusammengenommen mit N eine heterocyclische Gruppe mit 5 oder 6 C-Ringgliedern darstellen, R_3 und R_4 jeweils gleich oder verschieden sind und ausgewählt sind aus Wasserstoff, einem geradkettigen oder verzweigten Alkylrest mit 1 bis 6 C-Atomen, einem Cycloalkylrest mit 5 oder 6 C-Atomen, dem Phenylrest,
und worin R_5 Wasserstoff oder einen geradkettigen oder verzweigten C_1-C_6-Alkylrest darstellt.

Hierbei bedeuten verzweigte oder geradketige C_1-C_6-Alkylreste Methyl, Ethyl, iso- und n-Propyl, n- und iso-Butyl, n-Pentyl und n-Hexyl und Isomere hiervon.

Die Verbindungen eignen sich zur Behandlung der Schädigung von Neuronen infolge eines exzessiven Calciumüberschusses über NMDA-Rezeptorkanäle, insbesondere nach einer cerebralen Ischämie.

Die Erfindung umfasst auch die pharmazeutisch verträglichen Säureadditionssalze der obengenannten Verbindungen.

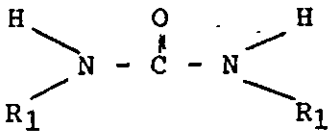
Gewisse 1-Amino-adamantane der Formel (I) sind an sich bekannt. So ist z.B. 1-Amino-3,5-dimethyladamantan Gegenstand der DE-PS 22 19 256 sowie der DE-PS 28 56 393.

Einige 3,5-disubstituierte 1-Amino-adamantane der Formel (I) sind in der US-PS 4 122 193 beschrieben. 1-Amino-3-ethyl-adamantan ist in der DE-PS 22 32 735 beschrieben.

Allgemein werden Verbindungen der Formel (I) hergestellt durch Alkylierung von Halogen-adamantan, vorzugsweise Brom- oder Chlor-adamantan. Nachfolgende weitere Halogenierung und Alkylierung liefert die einzelnen di- bzw. trisubstituierten Adamantane.

Die Einführung der Aminofunktion erfolgt entweder durch Oxidation mit Chromtrioxid und Bromierung mit HBr oder Bromierung mit Brom und Umsetzung mit Formamid und anschliessender Hydrolyse. Die Alkylierung der Aminofunktion kann nach allgemein bekannten Methoden durchgeführt werden. So lässt sich beispielsweise die Methylierung durch Reaktion mit Chlorameisensäuremethylester und nachfolgende Reduktion durchführen. Die Ethylgruppe kann durch Reduktion des entsprechenden Acetamids eingeführt werden.

Die Aminierung kann auch gemäss der US-A- 4 122 193 durch Umsetzung der entsprechenden 1-Halogen-3,5- oder -7-substituierten Verbindungen mit einem Harnstoffderivat der Formel

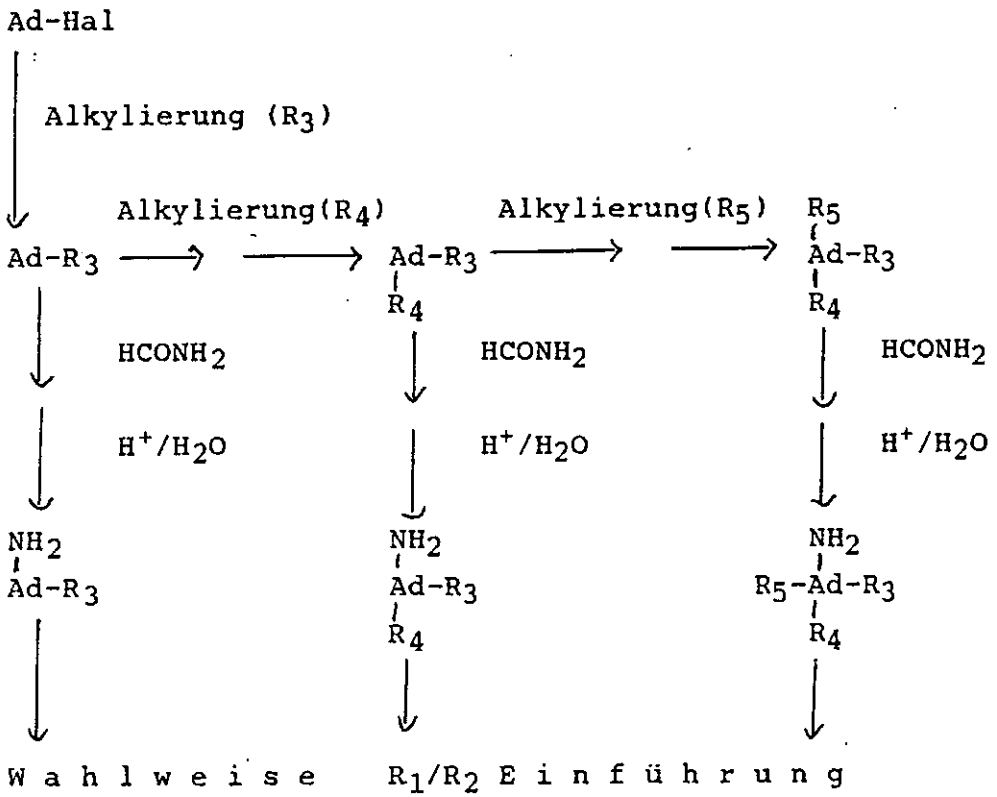


und, falls gewünscht, weiterer Alkylierung der Aminofunktion erfolgen.

Die Herstellung der Verbindungen gemäss Formel (I) ist im nachfolgenden Reaktionsschema dargestellt:

Reaktionsschema

Ad = Adamantylrest
Hal = Cl, Br



Die Alkylierung der Halogen-adamantane kann z.B. durch Friedel-Crafts-Reaktion (Einführung des Phenylrestes) bzw. durch Reaktion mit Vinylidenchlorid, anschliessender Reduktion und geeigneter Wittig-Reaktion der Aldehyde und deren Hydrierung oder durch Einschub von Ethylen und nachfolgender Alkylierung mit den entsprechenden Cupraten oder durch Einschub von Ethylen und Reduktion der Halogen-Alkyl-Adamantane oder durch Acylierung mit CO_2 und Reduktion der Carbonsäuren in an sich bekannter Weise erfolgen.

Die aus den obengenannten Druckschriften bekannten Verbindungen gemäss Formel (I) werden bislang als Mittel zur Behandlung von Morbus Parkinson und parkinsonähnlichen Erkrankungen verwendet. Ihre Wirkungsweise wird auf eine dopaminerge Beeinflussung des ZNS zurückgeführt, vermittelt entweder durch vermehrte Freisetzung oder durch Aufnahmehemmung der Transmittersubstanz Dopamin. Dadurch wird das Ungleichgewicht im Dopamin/Acetylcholinsystem aufgehoben.

In J.Pharmacol., 13, 163-164, 1982 wird der Effekt von dopaminergen Stimulantien, u.a. von 1-Amino-adamantan, auf das Koma-EEG untersucht. Es wird ferner gezeigt, daß Haloperidol die durch das Adamantan bewirkte Wiederherstellung von gestörter EEG-Aktivität aufhebt, da Haloperidol ein Dopamin-Antagonist ist.

In Japan J. Pharmacol. 39, 443-451, 1985, werden ebenfalls dopaminerge Substanzen untersucht, die akut zu einer EEG-Aktivierung bei ponsischämischen Ratten führen.

Ferner wird in Arzneimittelforschung 32, 1268-1273, 1982, die Wirkung von 1-Amino-adamantan bei Koma-Patienten untersucht und die Wirkung dieser Substanz auf den Katecholaminstoffwechsel beschrieben.

In der Veröffentlichung "British Medical Journal, 3, 272-273, 1973, wird das akute Verschwinden charakteristischer EEG-Veränderungen nach L-Dopa- und Amantadin-Therapie bei Patienten mit Jakob-Creutzfeldt-Disease erläutert, wobei die Wirksamkeit der Verbindungen auf deren dopaminergen Einfluß

zurückzuführen ist.

Die US-A 3 450 761 offenbart Amino-adamantane, u.a. 1-Amino-3-ethyl-5,7-dimethyl-adamantan, welche eine antivirale Wirkung aufweisen.

Im Gegensatz zu dieser Art von Erkrankungen liegt bei der cerebralen Ischämie eine pathophysiologische Situation vor, in der die neuronalen Erregungsmechanismen aus dem Gleichgewicht geraten. Dabei führt der exzessive Einstrom von Calcium durch N-Methyl-D-Aspartat(NMDA-)Rezeptorkanäle letztlich zur Zerstörung von Nervenzellen bestimmter Hirnareale (Rothmann & Olney, Trens Neurosci 10, 1987, 299ff). Für die Behandlung bzw. Behebung dieser pathologischen Situation scheint daher ein bezüglich der NMDA-Rezeptorkanäle antagonistisches Eingreifen erforderlich (Kemp et al., Trends Pharmacol., Sci. 8, 1987, 414ff).

Ein solches Eingreifen kann beispielsweise mit substituierten Fluor- und Hydroxyderivaten von Dibenzo-[a,d]-cyclohepten-5,10-imin erfolgen, die in der EP-A 0 264 183 beschrieben sind.

Diese heterocyclisch-aromatischen Verbindungen sind lipophiler Art und weisen NMDA-Rezeptorkanal-antagonistische sowie antikonvulsive Eigenschaften auf. Sie werden nach einem relativ aufwendigen Verfahren hergestellt, wobei Enantiomerenmischungen anfallen, die in die einzelnen optischen Antipoden aufgetrennt werden können.

Der vorliegenden Erfindung liegt die Aufgabe zugrunde, chemisch einfach zugängliche Verbindungen mit einer NMDA-Rezeptorkanal-antagonistischen und einer antikonvulsiven Wirkung bereitzustellen zur Verwendung bei der Prävention und Behandlung der cerebralen Ischämie.

Diese Aufgabe wird erfindungsgemäss gelöst durch die Verwendung der 1-Amino-adamantane der Formel (1),

Überraschend wurde gefunden, dass bei Verwendung dieser Verbindungen die Schädigung von Hirnzellen nach einer Ischämie verhindert werden kann. Die Adamantanderivate der Formel (I) eignen sich daher zur Prävention und zur Therapie cerebraler Ischämien nach Schlaganfall, Herzoperationen, Herzstillstand, Subarachnoidalblutungen, transienter cerebralischämischer Attacken, perinataler Asphyxie, Anoxie, Hypoglykämie, Apnoe und Morbus Alzheimer.

Beispiele erfindungsgemässer Verbindungen sind:

1-Amino-adamantan
1-Amino-3-phenyl-adamantan
1-Amino-methyl-adamantan
1-Amino-3,5-dimethyl-adamantan (Testverb.Nr. 1)
1-Amino-3-ethyl-adamantan (Testverbindung Nr. 2)
1-Amino-3-isopropyl-adamantan (Testverbindung Nr. 3)
1-Amino-3-n-butyl-adamantan
1-Amino-3,5-diethyl-adamantan (Testverbindung Nr. 4)
1-Amino-3,5-diisopropyl-adamantan
1-Amino-3,5-di-n-butyl-adamantan
1-Amino-3-methyl-5-ethyl-adamantan
1-N-Methylamino-3,5-dimethyl-adamantan(Testverb. Nr.5)
1-N-Ethyl-1-amino-3,5-dimethyl-adamantan(Testverb.Nr. 6)
1-N-Isopropyl-amino-3,5-dimethyl-adamantan
1-N,N-Dimethyl-amino-3,5-dimethyl-adamantan
1-N-Methyl-N-isopropyl-amino-3-methyl-5-ethyl-adamantan
1-Amino-3-butyl-5-phenyl-adamantan
1-Amino-3-pentyl-adamantan
1-Amino-3,5-dipentyl-adamantan
1-Amino-3-pentyl-5-hexyl-adamantan
1-Amino-3-pentyl-5-cyclohexyl-adamantan
1-Amino-3-pentyl-5-phenyl-adamantan
1-Amino-3-hexyl-adamantan
1-Amino-3,5-dihexyl-adamantan
1-Amino-3-hexyl-5-cyclohexyl-adamantan
1-Amino-3-hexyl-5-phenyl-adamantan
1-Amino-3-cyclohexyl-adamantan (Testverbindung Nr. 7)
1-Amino-3,5-dicyclohexyl-adamantan
1-Amino-3-cyclohexyl-5-phenyl-adamantan
1-Amino-3,5-diphenyl-adamantan
1-Amino-3,5,7-trimethyl-adamantan

1-Amino-3,5-dimethyl-7-ethyl-adamantan (Testverb. Nr. 8)
1-Amino-3,5-diethyl-7-methyl-adamantan,
deren N-Methyl-, N,N-Dimethyl-, N-Ethyl-, N-Propyl-,
1-N-Pyrrolidino- und 1-N-Piperidino-Derivate,
1-Amino-3-methyl-5-propyl-adamantan
1-Amino-3-methyl-5-butyl-adamantan
1-Amino-3-methyl-5-pentyl-adamantan
1-Amino-3-methyl-5-hexyl-adamantan
1-Amino-3-methyl-5-cyclohexyl-adamantan
1-Amino-3-methyl-5-phenyl-adamantan
1-Amino-3-ethyl-5-propyl-adamantan
1-Amino-3-ethyl-5-butyl-adamantan
1-Amino-3-ethyl-5-pentyl-adamantan
1-Amino-3-ethyl-5-hexyl-adamantan
1-Amino-3-ethyl-5-cyclohexyl-adamantan
1-Amino-3-ethyl-5-phenyl-adamantan
1-Amino-3-propyl-5-butyl-adamantan
1-Amino-3-propyl-5-pentyl-adamantan
1-Amino-3-propyl-5-hexyl-adamantan
1-Amino-3-propyl-5-cyclohexyl-adamantan
1-Amino-3-propyl-5-phenyl-adamantan
1-Amino-3-butyl-5-pentyl-adamantan
1-Amino-3-butyl-5-hexyl-adamantan
1-Amino-3-butyl-5-cyclohexyl-adamantan
sowie deren Säureadditionsverbindungen.

Bevorzugte Verbindungen der Formel (I) sind jene, worin R_1 und R_2 Wasserstoff bedeuten, wie z.B. 1-Amino-3-ethyl-5,7-dimethyl-adamantan, sowie Verbindungen, worin R_1, R_2, R_4 und R_5 Wasserstoff bedeuten, wie z.B. 1-Amino-3-cyclohexyl-adamantanund 1-Amino-3-ethyl-adamantan.

Weiterhin bevorzugte Verbindungen sind solche, worin R_1, R_2 und R_5 Wasserstoff bedeuten, wie z.B. 1-Amino-3-methyl-5-propyl- oder -5-butyl-adamantan, 1-Amino-3-methyl-5-hexyl-bzw. -cyclohexyl-adamantan oder 1-Amino-3-methyl-5-phenyladamantan.

Besonders bevorzugte Verbindungen sind 1-Amino-3,5-dimethyl-adamantan, 1-Amino-3,5-diethyl-adamantan, d.h. Verbindungen, worin R_1, R_2 und R_5 Wasserstoff bedeuten, sowie jene, worin R_1 und R_5 Wasserstoff, R_2 Methyl oder Ethyl und R_3 und R_4 jeweils Methyl bedeuten, wie z.B. 1-N-Methylamino-3,5-dimethyl-adamantan und 1-N-Ethylamino-3,5-dimethyladamantan.

Die Adamantanderivate der Formel (I) können als solche oder in Form ihrer pharmazeutisch verträglichen Säureadditions salze verabreicht werden. Hierzu zählen beispielsweise die Hydrochloride, Hydrobromide, Sulfate, Acetate, Succinate oder Tartrate, Additionsverbindungen mit Fumar-, Malein-, Zitronen- oder Phosphorsäure.

Die Verbindungen der Formel (I) werden in geeigneter Form in Mengen von etwa 0,01 bis 100 mg/kg verabreicht. Geeignete Darreichungsformen sind z.B. Kombinationen des Wirkstoffs mit üblichen pharmazeutischen Trägern und Hilfsmitteln in Form von Tabletten, Dragees, sterilen Lösungen oder Injektionen. Als pharmazeutisch verträgliche Träger können z.B. Lactose, Sucrose, Sorbit, Talcum, Stearinsäure, Magnesiumstearat, Gummiarabicum, Maisstärke oder Cellulose zusammen mit Verdünnungsmitteln wie Wasser, Polyethylenglykol u.ä. verwendet werden. Feste Darreichungsformen werden nach üblichen Methoden hergestellt und können bis zu 50 mg Wirkstoff/Einheit enthalten.

Die Wirksamkeit der Verbindungen der Formel (I) wird anhand der nachfolgenden pharmakologischen Untersuchungen aufgezeigt.

A. Verdrängung der TCP-Bindung

Phencyclidin (PCP), ein bekannter NMDA-Antagonist, bindet an den mit dem NMDA-Rezeptor assoziierten Ionenkanal und blockiert den Ionentransport (Garthwaite & Garthwaite, Neurosci. Lett.83, 1987, 241-246). Ferner gilt als nachgewiesen, dass PCP den Untergang von Nervenzellen als Folge cerebraler Ischämie bei Ratten zu verhindern vermag (Sauer et al., Neurosci. Lett. 91, 1988, 327-332).

Im folgenden wird untersucht, oh die Verbindungen der Formel (I) mit der Bindungsstelle für PCP interagieren. Hierzu Wird ^{3}H-TCP, ein Analogon von PCP, eingesetzt.

Eine Membranpräparation vom Rattencortex wird mit ^{3}H-TCP, einem Analogon von Phencyclidin (PCP), inkubiert (Quirion & Pert 1982, Eur.J.Pharmaccol. 83:155). Für Testverbindung Nr. 1: 1-Amino 3,5-dimethyladamantan wird die Wechselwirkung mit der TCP-Bindungsstelle im Kompetitionsexperiment ermittelt.

Dabei zeigt sich, dass Testverbindung Nr. 1 in der Lage ist, TCP hochwirksam aus der Bindung zu verdrängen. Der IC_{50}-Wert beträgt 89 nM. Daraus folgt, dass Testverbindung Nr. 1 an NMDA-Rezeptorkanäle bindet, und zwar dort, wo der NMDA-Antagonist PCP angreift.

B. Blockierung von NMDA-Rezeptorkanälen

Im folgenden Test wird gezeigt, dass die erfindungsgemässen Verbindungen der Formel (I) ebenso wie PCP den NMDA-Rezeptorkanal blockieren.

Im patch clamp-Experiment wird der Strom durch NMDA-aktivierte Membrankanäle kultivierter Rückenmarksneurone (Maus) gemessen (Hamill et al 1981, Pflügers Arch. 312: 85-100). Dabei wird das Stromsignal der Zelle nach Gabe von 20 µM NMDA über einen Zeitraum von 20 Sekunden integriert und als Kontrollantwort (A_c) gewertet. Bei der sich anschliessenden gemeinsamen Applikation von 20 µM NMDA und 6 µM eines Adamantanderivates kann die Stärke der Substanzwirkung als relative Änderung der Kontrollantwort, A/A_c, bestimmt werden (A = Testantwort).

Die Ergebnisse sind in nachfolgender Tabelle 1 zusammengefasst:

Tabelle 1

Verbindung Nr.	$1-A/A_c$	n
1	0,66±0,05	14
2	0,44±0,08	7
3	0,58±0,07	7
4	0,50±0,11	5
5	0,56±0,07	7
6	0,38±0,05	7
7	0,25±0,04	11
8	0,50±0,03	6
PCP	0,50±0,04	7
MK-801	0,60±0,05	22
Werte sind angegeben als Mittelwert ± S.E.M.		

Wie hieraus ersichtlich ist, sind die Amino-adamantanderivate der Formel (I) in der Lage, den NMDA-Rezeptorkanal zu blockieren, wie es auch für PCP (Bertolini et al., Neurosci. Lett. 84, 1988, 351-355) sowie für 5-Methyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imin (MK-801) (EP-A 0 264 183) beschrieben wurde.

C. Antikonvulsive Wirkung

Mäuse werden mit 4, 12, 36, 108 und 324 mg/kg der Testsubstanz ip-appliziert (5 Tiere je Dosis). Der supermaximale Elektroschocktest wurde 40 Minuten nach der Substanzgabe angewendet, um den Schutz der Substanz vor Krämpfen zu untersuchen. Die geschützten Tiere werden über alle Dosierungen aufaddiert (Score; Maximum = 25 Tiere).

Die Ergebnisse sind in nachfolgender Tabelle 2 angegeben.

Tabelle 2

Verbindung Nr.	Antikonvulsive Wirkung (Score)	Mittelwert	ED_{50} (mg/kg)
1	18		
	16		
	16		
	15	16,3	16
2	15		
	14		
	12	13,7	30
4	16		
	16		
	11	14,3	24
5	17		
	17	17,0	13
Standards:			
PCP	19	19,0	9
MK-801	25	25,0	<1

Die ED_{50}-Werte sind nach Litchfield und Wilcoxon (1949) geschätzt.

Wie hieraus ersichtlich ist, sind Amino-adamantanderivate der Formel (I) in der Lage, vor elektrisch induzierten Krämpfen zu schützen. Sie sind somit antikonvulsiv wirksam.

D. Korrelation zwischen Kanalblockade und antikonvulsiver Wirkung

Es wird geprüft, ob die Wirkung der getesteten Adamantanderivate 1-8 am NMDA-Rezeptorkanal (in vitro) mit der antikonvulsiven Wirkung (in vivo) im Zusammenhang steht. Dazu wird ein x-y Diagramm der beiden Testparameter erstellt, welches in Abbildung 1 dargestellt ist.

Hieraus kann entnommen werden, dass für die Adamantane der Formel (I) eine Korrelation zwischen der Blockade des NMDA-Rezeptorkanals und der antikonvulsiven Wirkung besteht.

E. Protektion vor cerebraler Ischämie

Bei Ratten werden beide Carotis-Arterien für 10 Minuten verschlossen und im gleichen Zeitraum der Blutdruck durch Blutentnahme auf 60-80 mg Hg abgesenkt (Smith et al. 1984, Acta Neurol. Scand. 69: 385, 401). Die Ischämie wird dann durch öffnen der Karotiden und Reinfusion des entnommenen Blutes beendet. Sieben Tage danach werden die Gehirne der Versuchstiere histologisch auf Zellveränderungen in der CA1-CA4-Region des Hippocampus untersucht und der prozentuale Anteil der Neuronenuntergänge ermittelt. Die Wirkung von Testverbindung Nr. 1 wird nach Einmalgabe von 5 mg/kg und 20 mg/kg ip eine Stunde vor der Ischämie geprüft.

Die Ergebnisse sind in nachfolgender Tabelle 3 zusammengefasst:

Tabelle 3

Areal	Kontrolle	Testverbindung Nr. 1	
		5 mg/kg (n = 5)	20 mg/kg (n = 6)
CA1	80,2±1,5	83,0±2,2	53,1±6,1**
CA3	3,6±1,1	7,3±1,8	2,7±1,0
CA4	1,4±0,4	3,7±1,7	0,6±0,3
Die Werte sind angegeben als Prozent der geschädigten Neuronen ± S.E.M. Signifikanz der Mittelwertdifferenz:			
**p < 0,01 (U-Test)			

Hieraus ergibt sich, dass präischämische Applikation von 20 mg/kg der Testverbindung Nr. 1 die postischämischen neuronalen Zellschäden im CA1-Areal des Rattenhippocampus statistisch signifikant reduziert. Unter der Behandlung werden physiologische Parameter (z.B. Blutdruck, Körpertemperatur) nicht verändert. Die Ergebnisse zeigen ferner, dass die Verbindungen gemäss Formel (I) eine neuroprotektive Wirkung bei cerebraler Ischämie haben.

Die Erfindung wird anhand der folgenden Beispiele erläutert.

Beispiel 1

Injektionslösung

Zur Herstellung einer 0,5%igen Lösung werden 0,5% Wirkstoff und 0,8% Natriumchlorid DAB 9 in bidestilliertem Wasser gelöst. Die Lösung wird durch ein Entkeimungsschichtenfilter filtriert, in 2-ml-Ampullen abgefüllt und 20 Minuten bei 120 °C im Autoklav heiss-sterilisiert.

Beispiel 2

Lösung

1% Wirkstoff wird in demineralisiertem Wasser gelöst. Die Lösung wird vor der Abfüllung filtriert.

Beispiel 3

Tabletten

1 Tablette besteht aus:	
Wirkstoff	10,0 mg
Milchzucker	67,5 mg
Mikrokristalliner Cellulose	18,0 mg
Talcum	4,5 mg
	100,0 mg

Die Substanzen werden gemischt und im Direkttablettierverfahren ohne Granulation zu Tabletten a 100 mg verpresst.

Beispiel 4

Dragees

Es werden, wie unter Tabletten beschrieben, 6 mm Dragee-Kerne mit einem Gewicht von 100 mg hergestellt. Die Hülle wird nach dem Zuckerdragierverfahren aufgetragen: Der Kern wird zunächst mit

Dragiersuspension angedeckt, dann mit Farbsirup gefärbt und schliesslich poliert.

Die Drageehülle besteht aus:

Zucker	65,0 mg
Talcum	39,0 mg
Calciumcarbonat	13,0 mg
Gummiarabicum	6,5 mg
Maisstärke	3,7 mg
Schellack	1,1 mg
Polyethylenglykol 6000	0,2 mg
Magnesia usta	1,3 mg
Farbstoff	0,2 mg
	130,0 mg
Gesamtdragee-Gewicht = 230 mg	

Beispiel 5

Zur Herstellung einer 0,01%igen Infusionslösung werden 0,01% Wirkstoff und 5% Laevulose in bidestilliertem Wasser gelöst. Die Lösung wird durch Entkeimungsfilter filtriert, in 500 ml Infusionsflaschen abgefüllt und sterilisiert.

Das Beispiel bezieht sich auf 50 mg Wirkstoff pro Einzeldosis.

Beispiel 6

Synthese von 1-Amino-3-isopropyl-adamantan-Hydrochlorid (Testverbindung Nr. 3)

A. Die Darstellung von Adamantancarbonsäuremethylester(I)

1,0 Mol Adamantancarbonsäure werden in 600 ml Methanol gerührt. Unter Eiskühlung werden innerhalb 1h 1,53 Mol Acetylchlorid zugetropft. Das Eisbad wird entfernt und das Reaktionsgemisch auf Raumtemperatur kommen lassen, anschliessend wird 3h unter Rückfluss erhitzt. Das Reaktionsgemisch wird im Vakuum eingeengt und destilliert. (97% Ausbeute)

B. Darstellung von 2-Adamantyl-propan-2-ol(II)

0,5 Mol Magnesiumspäne werden in 50 ml absolutem Ether vorgelegt und 0,5 Mol Methyliodid unter Feuchtigkeitsausschluss so zugetropft, dass der Ether siedet. Anschliessend erwärmt man auf dem Wasserbad bis alles Magnesium gelöst ist.

Zu dieser Lösung tropft man bei Raumtemperatur eine Lösung von 0,2 Mol Adamantancarbonsäuremethylester(I) in absolutem Ether. Nach erfolgter Zugabe erhitzt man 3h zum Rückfluss. Nach dem Abkühlen hydrolysiert man mit Eis und versetzt mit Ammoniumchloridlösung bis der Niederschlag gelöst ist. Die Etherphase wird abgetrennt, die wässrige Phase 2x mit Ether gewaschen und die vereinigten organischen Phasen mit Natriumbicarbonat-Lösung gewaschen, getrocknet und im Vakuum eingeengt. (Ausbeute 93%)

C. Darstellung von Isopropenyl-adamantan(III)

0,25 Mol 2-Adamantyl-propan-2-ol(II) werden in 500 ml Essigsäureanhydrid bei 160 °C 12h gerührt. Anschliessend wird das Reaktionsgemisch auf 1 l Eiswasser gegossen und mit Ether extrahiert. Die vereinigten organischen Phasen werden mit Magnesiumsulfat getrocknet, filtriert und im Vakuum eingeengt. Der Rückstand wird im Vakuum destilliert. (Ausbeute 66%)

D. Darstellung von Isopropyl-adamantan(IV)

0,074 Mol Isopropenyl adamantan(III) werden in 100 ml absolutem Ethanol gelöst. Man gibt 4 g Palladium (5% auf Aktivkohle) zu und hydriert 24 h bei Raumtemperatur unter Rühren. Danach wird vom

Katalysator abfiltriert und das Lösungsmittel im Vakuum entfernt. (Ausbeute 91%)

E. Darstellung von 1-Brom-3-isopropyl-adamantan(V)

0,034 Mol Isopropyl-adamantan(IV) werden mit dem zehnfachen Überschuss an Brom versetzt (0,33 Mol). Man erwärmt langsam und rührt 4h unter Rückfluss. Anschliessend lässt man abkühlen und giesst auf Eiswasser. Das überschüssige Brom wird mit Natriumsulfit zersetzt, bis die wässrige Lösung entfärbt ist. Danach extrahiert man mit Ether, wäscht die vereinigten organischen Phasen mit Natriumbicarbonat-Lösung, trocknet mit Magnesiumsulfat, filtriert und engt im Vakuum ein. Der erhaltene Rückstand wird aus Methanol umkristallisiert. (Ausbeute 83%)

F. Darstellung von 1-Formyl-amido-3-isopropyl-adamantan(VI)

0,028 Mol 1-Brom-3-isopropyl-adamantan(V) werden mit 40 ml Formamid 12 h zum Rückfluss erhitzt. Nach dem Abkühlen wird das Reaktionsgemisch auf Wasser gegossen und mit Dichlormethan extrahiert. Die vereinigten organischen Phasen werden mit Magnesiumsulfat getrocknet, filtriert und im Vakuum eingeengt. (Ausbeute 82%)

G. Darstellung von 1-Amino-3-isopropyl-adamantan-Hydrochlorid

0,023 Mol 1-Formyl-amido-3-isopropyl-adamantan(VI) werden mit 100 ml 15%iger Salzsäure versetzt und 24h zum Sieden erhitzt. Nach dem Abkühlen wird der Niederschlag abfiltriert und aus Isopropanol umkristallisiert. (Ausbeute 57%)

Beispiel 7

Synthese von 1-Amino-3-cyclohexyl-adamantan-Hydrochlorid (Testverbindung Nr. 7)

A. Darstellung von 1-Phenyl-adamantan(I)

0,068 Mol Eisen(III)-chlorid werden in 20 ml absolutem Benzol zum Sieden erhitzt. Unter Rühren werden 0,0186 Mol 1-Brom-adamantan, in 30 ml abs. Benzol gelöst, zugetropft. Danach wird 3 h zum Sieden erhitzt. Das Reaktionsgemisch wird nach dem Abkühlen auf Eis/Salzsäure gegossen, die organische Phase abgetrennt und die wässrige Phase noch zwei Mal mit Benzol extrahiert. Die vereinigten organischen Phasen werden mit Wasser gewaschen, mit Calciumchlorid getrocknet, filtriert und im Vakuum eingeengt. Der Rückstand wird aus Methanol umkristallisiert. (Ausbeute 80%)

B. Darstellung von 1-Hydroxy-3-phenyl-adamantan(II)

Zu einer Lösung aus 0,03 Mol Chromtrioxid in 20 ml Eisessig und 20 ml Essigsäureanhydrid werden bei 0 °C 0,0095 Mol 1-Phenyl-adamantan zugegeben und 24 h bei 4 °C gerührt. Das Reaktionsgemisch wird dann auf Wasser gegossen und drei Mal mit Pentan extrahiert. Die organische Phase wird mit gesättigter Natriumchlorid-Lösung gewaschen, über Magnesiumsulfat getrocknet, filtriert und im Vakuum eingeengt. Der Rückstand wird mit 20 ml 2N NaOH und 50 ml Methanol hydrolysiert. Das Methanol wird anschliessend im Vakuum entfernt und der Rückstand mit Wasser verdünnt. Dann wird drei Mal mit Ether extrahiert. Die organische Phase wird gtrocknet, filtriert und im Vakuum eingeengt. Der Rückstand wird aus Cyclohexan umkristallisiert. (Ausbeute 50%)
Lit.: H.Stetter, M.Schwarz u. A.Hirschhorn, Chem.Ber. (1959), 92,1629-35.

C. Darstellung von 1-Brom-3-phenyl-adamantan(III)

0,03 Mol 3-Phenyl-adamantanol(II) werden mit 100 ml 40%iger HBr in Eisessig 20min bei 60 °C und 30min bei Raumtemperatur gerührt. Das Reaktionsgemisch wird anschliessend mit Wasser verdünnt und mit Ether extrahiert. Die vereinigten organischen Extrakte werden mit Natriumchlorid-Lösung gewaschen, mit Magnesiumsulfat getrocknet, filtriert und im Vakuum eingeengt. Der Rückstand wird aus Methanol umkristallisiert. (Ausbeute 68%)
Lit.: W.Fischer u. C.A.Grog, Helvetica Chim.Acta (1976), 59,1953.

D. Darstellung von 1-Formyl-amido-3-phenyl-adamantan(IV)

0,03 Mol 1-Brom-3-phenyl-adamantan(III) werden mit 50 ml Formamid 12h zum Rückfluss erhitzt. Nach dem Abkühlen giesst man das Reaktionsgemisch auf Wasser und extrahiert mit Dichlormethan. Die vereinigten organischen Phasen werden mit Magnesiumsulfat getrocknet, filtriert ud eingeengt. (Ausbeute 80%)

E. Darstellung von 1-Amino-3-phenyl-adamantan-Hydrochlorid(V)

0,02 Mol 1-Formyl-amido-3-phenyl-adamantan(IV) werden mit 100ml 15%iger Salzsäure 24h zum Sieden erhitzt. Nach dem Abkühlen wird der Niederschlag abfiltriert und aus Isopropanol umkristallisiert. (Ausbeute 60%)

F. Darstellung von 1-Amino-3-cyclohexyl-adamantan(VI)

0,011 Mol 1-Amino-3-phenyl-adamantan(V) werden in 150ml Eisessig gelöst, mit 0,3 g Platinoxid (1% of Aktivkohle) versetzt und bei 3 bar Wasserstoffdruck in einer Parr-Apparatur bei 35 °C hydriert. Anschliessend wird der Katalysator abfiltriert und das Filtrat eingeengt. Der Rückstand wird mit Methanol aufgenommen und das Produkt mit Ether ausgefällt, abgesaugt und getrocknet. (Ausbeute 70%)

Beispiel 8

Synthese von 1-Amino-3,5-dimethyl-7-ethyl-adamantan-Hydrochlorid (Testverbindung Nr. 8)

A. Darstellung von 1-Brom-3,5-dimethyl-adamantan(I)

0,5 Mol 1,3-Dimethyl-adamantan werden mit dem zehnfachen Überschuss an Brom versetzt (5 Mol). Man erwärmt langsam und rührt 4h unter Rückfluss. Anschliessend lässt man abkühlen und giesst auf Eiswasser. Das überschüssige Brom wird mit Natriumsulfit zersetzt, bis die wässrige Lösung entfärbt ist. Danach extrahiert man mit Ether, wäscht die vereinigten organischen Phasen mit Natriumbicarbonat-Lösung, trocknet mit Magnesiumsulfat, filtriert und engt im Vakuum ein. Der erhaltene Rückstand wird aus Methanol umkristallisiert. (Ausbeute 83%)

B. Darstellung von 1-(2-Brom-ethyl)-3,5-dimethyl-adamantan(II)

1,4 Mol 1-Brom-3,5-dimethyl-adamantan(I) werden bei -75 °C in Hexan mit 0,6 Mol Aluminiumbromid versetzt. Danach leitet man 20 bis 30 Minuten Ethylen durch die Lösung, rührt 5min. nach und giesst das Reaktionsgemisch auf Eiswasser. Man extrahiert mit Ether, trocknet die organische Phase und engt diese ein. Der Rückstand wird aus Methanol umkristallisiert. (Ausbeute 48%)

C. Darstellung von 1,3-Dimethyl-5-ethyl-adamantan(III)

0,5 Mol 1-(2-Brom-ethyl)-3,5-dimethyl-adamantan(II) werden in Toluol gelöst und mit 0,55 Mol Natrium-bis(2-methoxyethoxy)-dihydro-aluminat versetzt und 3h zum Sieden erhitzt. Nach dem Hydrolysieren wird die organische Phase abgetrennt, mit Magnesiumsulfat getrocknet und im Vakuum eingeengt. Der Rückstand wird durch Vakuumdestillation gereinigt. (Ausbeute 86%)

D. Darstellung von 1-Brom-3,5-dimethyl-7-ethyl-adamantan(IV)

0,4 Mol 1,3-Dimethyl-5-ethyl-adamantan(III) werden mit dem zehnfachen Überschuss an Brom versetzt (4 Mol). Man erwärmt langsam und rührt 4h unter Rückfluss. Anschliessend lässt man abkühlen und giesst auf Eiswasser. Das überschüssige Brom wird mit Natriumsulfit zersetzt, bis die wässrige Lösung entfärbt ist. Danach extrahiert man mit Ether, wäscht die vereinigten organischen Phasen mit Natriumbicarbonat-Lösung, trocknet mit Magnesiumsulfat, filtriert und engt im Vakuum ein. Der erhaltene Rückstand wird aus Methanol umkristallisiert. (Ausbeute 86%)

E. Darstellung von 1-Formyl-amido-3,5-dimethyl-7-ethyl-adamantan(V)

0,2 Mol 1-Brom-3,5-dimethyl-7-ethyl-adamantan(IV) werden mit 150 ml Formamid 12h zum Rückfluss erhitzt. Nach dem Abkühlen wird das Reaktionsgemisch auf Wasser gegossen und mit Dichlormethan extrahiert. Die vereinigten organischen Phasen werden mit Magnesiumsulfat getrocknet, filtriert und im Vakuum eingeengt. (Ausbeute 82%)

F. Darstellung des 1-Amino-3,5-dimethyl-7-ethyl-adamantan-Hydrochlorids(VI)

0,2 Mol 1-Formyl-amido-3,5-dimethyl-7-ethyl-adamantan(V) werden mit 100 ml 15%iger Salzsäure versetzt und 24h zum Sieden erhitzt. Nach dem Abkühlen wird der Niederschlag abfiltriert und aus Isopropanol umkristallisiert. (Ausbeute 57%)

Beispiel 9

Synthese von 1-N-Methylamino-3,5-dimethyl-adamantan (Testverbindung Nr. 5)

0,1 Mol des entsprechend substituierten Amino-adamantans (1-Amino-3,5-dimethyl-adamantan) werden mit 0,15 Mol Chlorameisensäureethylester und Kaliumcarbonat in Aceton gelöst und 8h zum Rückfluss erhitzt. Nach dem Abkühlen wird filtriert, das Lösungsmittel abgezogen und der Rückstand getrocknet. Das Rohprodukt (0,05 Mol) wird mit 0,1 Mol Natrium-bis-(2-methoxy-ethoxy)-dihydroaluminat in Toluol versetzt und 3h zum Sieden erhitzt. Nach dem Abkühlen wird mit verd. HCl hydrolysiert, die organische Phase getrocknet und eingeengt. Das Rohprodukt wird durch Destillation gereinigt.

Beispiel 10

Synthese von 1-Amino-3-ethyl-5-phenyl-adamantan

A. Darstellung von 1-Brom-3-ethyl-adamantan(I)

0,034 Mol Ethyl-adamantan werden mit dem zehnfachen Überschuss an Brom versetzt (0,33 Mol). Man erwärmt langsam und rührt 4h unter Rückfluss. Anschliessend lässt man abkühlen und giesst auf Eiswasser. Das überschüssige Brom wird mit Natriumsulfit zersetzt, bis die wässrige Lösung entfärbt ist. Danach extrahiert man mit Ether, wäscht die vereinigten organischen phasen mit Natriumbicarbonat-Lösung, trocknet mit Magnesiumsulfat, filtriert und engt im Vakuum ein. Der erhaltene Rückstand wird aus Methanol umkristallisiert. (Ausbeute 83%)

B. Darstellung von 1-Ethyl-3-phenyl-adamantan(II)

0,068 Mol Eisen(III)-chlorid werden in 20 ml absolutem Benzol zum Sieden erhitzt. Unter Rühren werden 0,0186 Mol 1-Brom-3-ethyl-adamantan(I), in 30 ml abs. Benzol gelöst, zugetopft. Danach wird 3h zum Sieden erhitzt. Das Reaktionsgemisch wird nach dem Abkühlen auf Eis/Salzsäure gegossen, die organische Phase abgetrennt und die wässrige Phase noch zwei Mal mit Benzol extrahiert. Die vereinigten organischen Phasen werden mit Wasser gewaschen, mit Calciumchlorid getrocknet, filtriert und im Vakuum eingeengt. Der Rückstand wird aus Methanol umkristallisiert. (Ausbeute 80%)

C. Darstellung von 1-Ethyl-3-hydroxy-5-phenyl-adamantan(III)

Zu einer Lösung aus 0,03 Mol Chromtrioxid in 20 ml Eisessig und 20 ml Essigsäureanhydrid werden bei 0 °C 0,0095 Mol 1-Ethyl-3-phenyl-adamantan(II) zugegeben und 24h bei 4 °C gerührt. Das Reaktionsgemisch wird dann auf Wasser gegossen und drei Mal mit Pentan extrahiert. Die organische Phase wird mit gesättigter Natriumchlorid-Lösung gewaschen, über Magnesiumsulfat getrocknet, filtriert und im Vakuum eingeengt. Der Rückstand wird mit 20 ml 2N NaOH und 50 ml Methanol hydrolysiert. Das Methanol wird anschliessend im Vakuum entfernt und der Rückstand mit Wasser verdünnt. Dann wird drei Mal mit Ether extrahiert. Die organische Phase wird getrocknet, filtriert und im Vakuum eingeengt. Der Rückstand wird aus Cyclohexan umkristallisiert. (Ausbeute 50%) Lit.: H.Stetter, M.Schwarz u. A.Hirschhorn, Chem. Ber. (1959), 92, 1629-35

D. Darstellung von 1-Brom-3-ethyl-5-phenyl-adamantan(IV)

0,03 Mol 1-Ethyl-3-hydroxy-5-phenyl-adamantan(III) werden mit 100 ml 40%iger HBr in Eisessig 20min. bei 60 °C und 30 min bei Raumtemperatur gerührt. Das Reaktionsgemisch wird anschliessend mit Wasser verdünnt und mit Ether extrahiert. Die vereinigten organischen Extrakte werden mit Natriumchlorid-Lösung gewaschen, mit Magnesiumsulfat getrocknet, filtriert und im Vakuum eingeengt. Der Rückstand wird aus Methanol umkristallisiert. (Ausbeute 68%) Lit.: W.Fischer u. C.A.Grog, Helvetica Chim.Acta (1976), 59, 1953

E. Darstellung von 1-N-Formyl-3-ethyl-5-phenyladamantan(V)

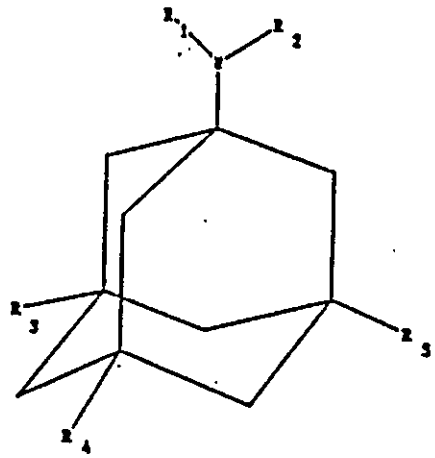
0,03 Mol 1-Ethyl-3-hydroxy-5-phenyl-adamantan(IV) werden mit 50 ml Formamid 12h zum Rückfluss erhitzt. Nach dem Abkühlen giesst man das Reaktionsgemisch auf Wasser und extrahiert mit Dichlormethan. Die vereinigten organischen Phasen werden mit Magnesiumsulfat getrocknet, filtriert und eingeengt. (Ausbeute 80%)

F. Darstellung von 1-Amino-3-ethyl-5-phenyl-adamantan-Hydrochlorid(VI)

0,02 Mol 1-N-Formyl-3-ethyl-5-phenyl-adamantan(V) werden mit 100 ml 15%iger Salzsäure 24h zum Sieden erhitzt. Nach dem Abkühlen wird der Niederschlag abfiltriert und aus Isopropanol umkristallisiert. (Ausbeute 60%)

Patentansprüche

1. Verwendung von Adamantan-Derivaten der allgemeinen Formel



(I)

worin R_1 und R_2 gleich oder verschieden sind und Wasserstoff oder geradkettige oder verzweigte Alkylgruppen mit 1 bis 6 C-Atomen bedeuten oder zusammengenommen mit N eine heterocyclische Gruppe mit 5 oder 6 Ringgliedern darstellen,
R_3 und R_4 jeweils gleich oder verschieden sind und ausgewählt sind aus Wasserstoff, einem geradkettigen oder verzweigten Alkylrest mit 1 bis 6 C-Atomen, einem Cycloalkylrest mit 5 oder 6 C-Atomen, dem Phenylrest,
und worin R_5 Wasserstoff oder einen geradkettigen oder verzweigten C_1-C_6-Alkylrest darstellt,
sowie deren pharmazeutisch verträglichen Salze,
zur Herstellung eines Medikaments zur Behandlung der Schädigung von Hirnzellen infolge eine cerebralen Ischämie.

2. Verwendung gemäss Anspruch 1, wobei R_1, R_2 und R_5 Wasserstoff bedeuten.

3. Verwendung gemäss Anspruch 2, wobei R_1, R_2 und R_5 Wasserstoff und R_3 und R_4 Methyl bedeuten.

4. Verwendung gemäss Anspruch 2, wobei R_1, R_2 und R_5 Wasserstoff und R_3 und R_4 Ethyl bedeuten.

5. Verwendung gemäss Anspruch 1, wobei R_1, R_2, R_4 und R_5 Wasserstoff und R_3 Ethyl, Isopropyl oder Cyclohexyl bedeuten.

6. Verwendung gemäss Anspruch 1, wobei R_2 und R_5 Wasserstoff bedeuten.

7. Verwendung gemäss Anspruch 6, wobei R_3 und R_4 Methyl, R_2 und R_5 Wasserstoff und R_1 Methyl oder Ethyl bedeuten.

8. Verwendung gemäss Anspruch 1, worin R_1 und R_2 Wasserstoff bedeuten.

9. Verwendung gemäss Anspruch 8, worin R_1 und R_2 Wasserstoff,R_3 Ethyl und R_5 und R_4 Methyl bedeuten.

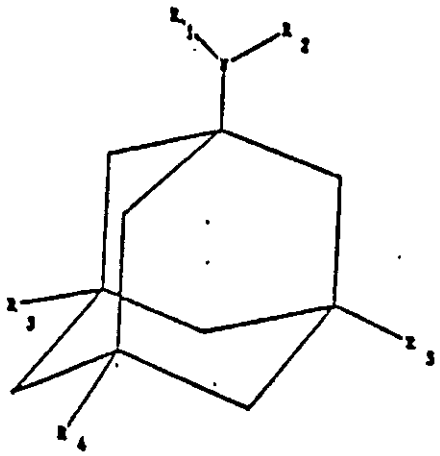
10. Verwendung gemäß Anspruch 1, wobei das Adamantanderivat 1-Amino-3-ethyl-5,7-dimethyl-adamantan ist.

11. Verwendung von Adamantan-Derivaten, wie sie in den Ansprüchen 1-9 offenbart werden, zur Herstellung eines Medikaments zur Behandlung von Morbus Alzheimer.

12. 1-Amino-3-cyclohexyl-adamantan.

Claims

1. The use of adamantane derivatives corresponding to the following general formula



(I)

wherein R_1 and R_2 are identical or different and stand for hydrogen or straight chain or branched alkyl groups having 1 to 6 carbon atoms or together with N represent a heterocyclic group having 5 or 6 ring members,
R_3 and R_4 are identical or different and are selected from hydrogen, a straight chain or branched alkyl group having 1 to 6 carbon atoms, a cycloalkyl group having 5 or 6 carbon atoms or the phenyl group and
R_5 denotes hydrogen or a straight chain or branched C_1-C_6-alkyl group
and their pharmaceutically acceptable salts for the preparation of a medicament for the treatment of damage to brain cells due to cerebral ischaemia.

2. Use according to Claim 1 wherein R_1, R_2 and R_5 denote hydrogen.

3. Use according to Claim 2 wherein R_1, R_2 and R_5 denote hydrogen and R_3 and R_4 denote methyl.

4. Use according to Claim 2 wherein R_1, R_2 and R_5 denote hydrogen and R_3 and R_4 denote ethyl.

5. Use according to Claim 1 wherein R_1, R_2, R_4 and R_5 denote hydrogen and R_3 denotes ethyl, isopropyl or cyclohexyl.

6. Use according to Claim 1 wherein R_2 and R_5 denote hydrogen.

7. Use according to Claim 6 wherein R_3 and R_4 denote methyl, R_2 and R_5 denote hydrogen and R_1 denotes methyl or ethyl.

8. Use according to Claim 1 wherein R_1 and R_2 denote hydrogen.

9. Use according to Claim 8 wherein R_1 and R_2 denote hydrogen, R_3 denotes ethyl and R_5 and R_4 denote methyl.

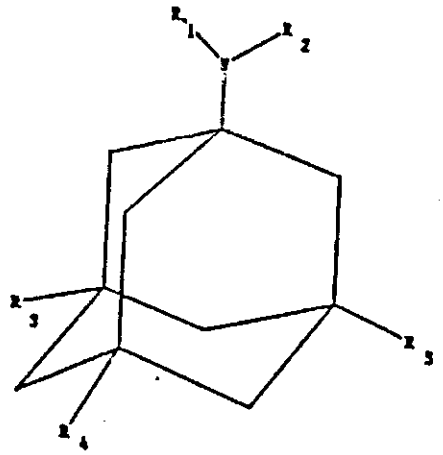
10. Use according to Claim 1, wherein the adamantane derivative is 1-amino-3-ethyl-5,7-dimethyl-adamantane.

11. Use of adamantane derivatives as disclosed in claims 1 to 9 for the preparation of a medicament for the treatment of Alzheimer's disease.

12. 1-Amino-3-cyclohexyl-adamantane.

Revendications

1. Utilisation de dérivés d'adamantane de formule générale :



(I)

dans laquelle R_1 et R_2 sont identiques ou différents et représentent l'hydrogène ou des groupes alkyles à chaîne droite ou ramifiée en C_1-C_6 ou bien, pris avec l'atome d'azote, un groupe hétérocyclique à 5 ou 6 chaînons, R_3 et R_4 sont identiques ou différents et représentent chacun l'hydrogène, un reste alkyle à chaîne droite ou ramifiée en C_1-C_6, un groupe cycloalkyle en C_5 ou C_6, le reste phényle, et dans laquelle R_5 représente l'hydrogène ou un reste alkyle à chaîne droite ou ramifiée en C_1-C_6. et leurs sels acceptables en pharmacie, pour la préparation d'un médicament pour le traitement des lésions des cellules cérébrales résultant d'une ischémie cérébrale.

2. Utilisation selon la revendication 1, dans laquelle R_1, R_2 et R_5 représentent l'hydrogène.

3. Utilisation selon la revendication 2, dans laquelle R_1, R_2 et R_5 représentent l'hydrogène et R_3 et R_4 représentent des groupes méthyles.

4. Utilisation selon la revendication 2, dans laquelle R_1, R_2 et R_5 représentent l'hydrogène et R_3 et R_4 représentent des groupes éthyles.

5. Utilisation selon la revendication 1, dans laquelle R_1, R_2, R_4 et R_5 représentent l'hydrogène et R_3 représente un groupe éthyle, isopropyle ou cyclohexyle.

6. Utilisation selon la revendication 1, dans laquelle R_2 et R_5 représentent l'hydrogène.

7. Utilisation selon la revendication 6, dans laquelle R_3 et R_4 représenent des groupes méthyles, R_2 et R_5 représentent l'hydrogène et R_1 représente un groupe méthyle ou éthyle.

8. Utilisation selon la revendication 1, dans laquelle R_1 et R_2 représentent l'hydrogène.

9. Utilisation selon la revendication 8, dans laquelle R_1 et R_2 représentent l'hydrogène, R_3 représente un groupe éthyle et R_5 et R_4 représentent des groupes méthyles.

10. Utilisation selon la revendication 1, dans laquelle le dérivé d'adamantane est le 1-amino-3-éthyl-5,7-diméthyl-adamantane.

11. Utilisation de dérivés d'adamantane selon les revendications 1-9, pour la préparation d'un médicament pour le traitement de la maladie d'Alzheimer.

12. Le 1-amino-3-cyclohexyl-adamantane.

Abbildung 1

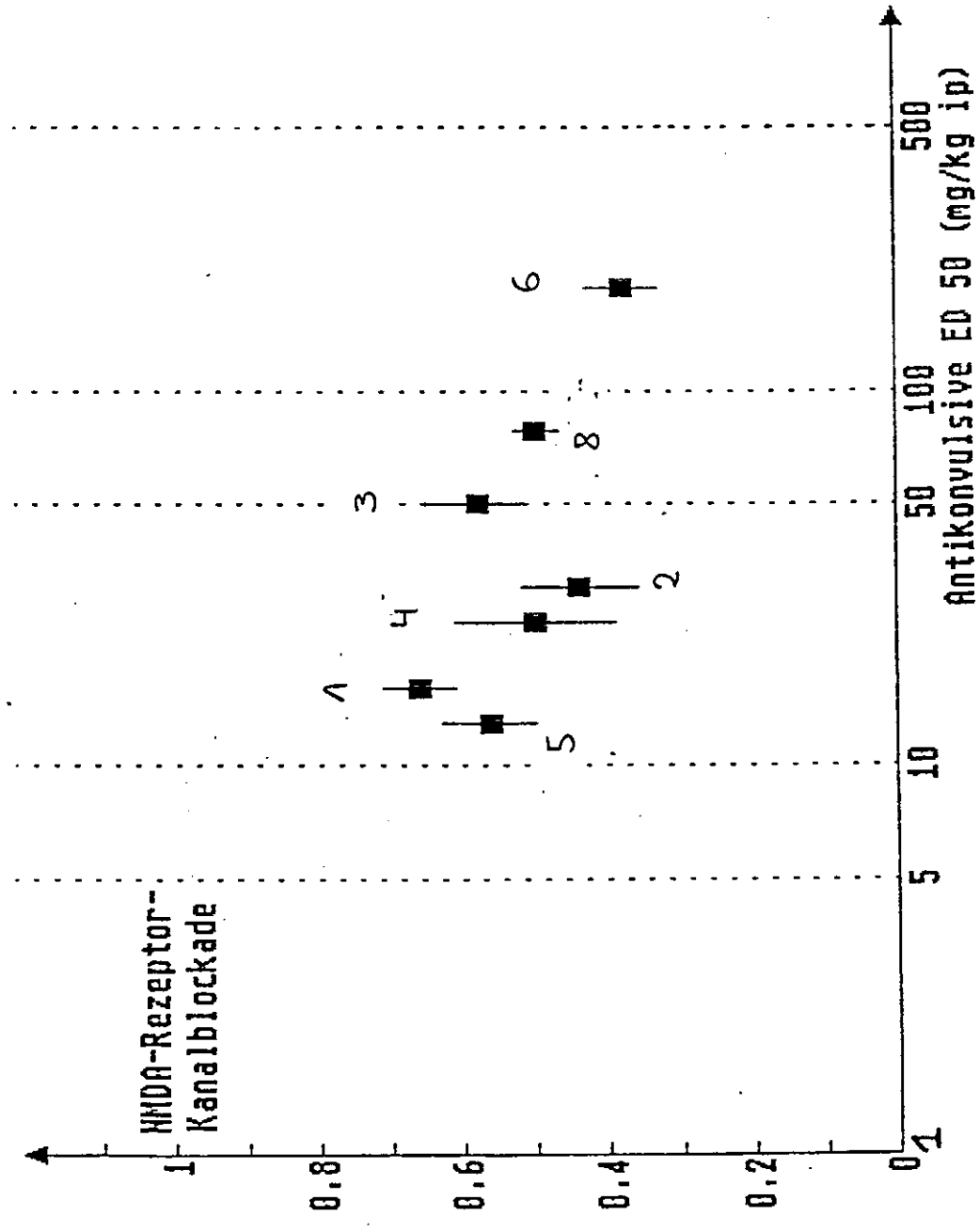

NMDA-Rezeptor-Kanalblockade
1
0,8
0,6
0,4
0,2
0
Antikonvulsive ED 50 (mg/kg ip)
1
5
10
50
100
500
1
2
3
4
5
6
8

EXHIBIT J

TABLE OF CONTENTS

Defenses Raised in Notice Letters

1. In their Notice Letters, the Generic Companies argued a variety of defenses including non-infringement and invalidity of the '703 patent under 35 U.S.C. §§ 101, 102, 103, 112, 156, and 305[1].

A. Non-Infringement

2. Numerous Generic Companies argued non-infringement[2].

3. With respect to non-infringement, Mylan argued that it "does not infringe or induce infringement of the independent claims because Mylan does not intend to sell its proposed memantine hydrochloride tablets for the claimed methods, but rather for treatment of moderate to severe dementia of the Alzheimer's type." Mylan's Notice Letter at FRX-AT-03490151. Mylan argued further that direct infringement would require "the actual showing that the administration reduces or prevents neurodegeneration in . . . patients [with Alzheimer's disease]" and "there does not appear to be evidence establishing its treatment of the nerve cells in humans." *Id.* Mylan also argued that its proposed product would not "infringe under the doctrine of equivalents" because "[c]erebral ischemia and an imbalance of neuronal stimulation are neither exclusively associated with Alzheimer's disease nor defined by it." *Id.* at FRX-AT-03490152.

[1] FRX-AT-03490244-277 (Cobalt Labs, Inc.'s Notice Letter); *see also* FRX-AT-03490110-131 (Lupin Pharma's Notice Letter); *see also* FRX-AT-03488151-168 (TEVA Pharmaceuticals USA Inc.'s Notice Letter); *see also* FRX-AT-03169274-299 (Upsher-Smith Laboratories' Notice Letter); *see also* FRX-AT-03490173-243 (Wockhardt USA's Notice Letter); *see also* FRX-AT-02588339-346 (Barr Laboratories Inc.'s Notice Letter); *see also* FRX-AT-03490041-068 (Dr. Reddy's Limited's Notice Letter); *see also* FRX-AT-03490069-109 (Genpharm LP's Notice Letter); *see also* FRX-AT-03490296-318 (Interpharm Inc.'s Notice Letter); *see also* FRX-AT-03490132-172 (Mylan Pharmaceuticals Inc.'s Notice Letter); *see also* FRX-AT-03169490-503 (Sun India's Notice Letter); *see also* FRX-AT-03169532-547 (Synthon's Notice Letter); *see also* FRX-AT-03169548-561 (Apotex's Notice Letter); *see also* FRX-AT-03483932-947 (Ranbaxy Laboratories Ltd.'s Notice Letter); *see also* FRX-AT-03169232-273 (Orchid Healthcare's Notice Letter).

[2] Teva's Notice Letter at FRX-AT-03488155-156; *see also* Cobalt's Notice Letter at FRX-AT-03490262-271; *see also* Barr's Notice Letter at FRX-AT-02588343-346; *see also* Orchid's Notice Letter at FRX-AT-03169257-259; *see also* Lupin's Notice Letter at FRX-AT-03490125-127; *see also* Upsher-Smith's Notice Letter at FRX-AT-03169287-291; *see also* Wockhardt's Notice Letter at FRX-AT-03490231-238; *see also* Genpharm's Notice Letter at FRX-AT-03490079-080; *see also* Mylan's Notice Letter at FRX-AT-03490147-152; *see also* Ranbaxy's Notice Letter at FRX-AT-03483942; *see also* Sun India's Notice Letter at FRX-AT-03169501-503; *see also* Dr. Reddy's Notice Letter at FRX-AT-03490056-060; *see also* Synthon's Notice Letter at FRX-AT-03169535-537; *see also* Apotex's Notice Letter at FRX-AT-03169557.

B. Invalidity: § 101 – Utility

4. At least one Generic Company argued that the claims of the '703 patent were invalid for lacking utility under § 101[3]. Specifically, Orchid argued that the '703 patent was invalid for lack of utility (as an alternative to its § 112 enablement argument) because:

> [t]he '703 patent specification does not contain data supporting the claimed use of memantine to prevent or treat neuronal degeneration resulting from cerebral ischemia in a patient with Alzheimer's disease or, alternatively, 'the treatment of Alzheimer's disease' alone. There is no data of the sort set forth in the prior art references described . . . and [i]n fact, there is no data of any type evidencing that memantine could be used to treat dementia.

Id. at FRX-AT-03169272. Orchid further argued that the Federal Circuit has held that a patent may be invalid under either § 112 or § 101 "'when there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention.'" *Id.* at FRX-AT-03169271 (quoting *In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999).

C. Invalidity: § 102 – Anticipation

5. At least two Generic Companies argued that the claims of the '703 patent were invalid as anticipated under § 102[4].

6. Synthon argued the '703 patent was anticipated under § 102(b) by Fleischhacker. Synthon's Notice Letter at FRX-AT-03169538. Specifically, Synthon argued that Fleischhacker, entitled "Memantine in the Treatment of Senile Dementia of the Alzheimer's type," "places the average artisan in possession of a method that comprises orally administering memantine to an Alzheimer's patient using any reasonable pharmaceutical amount." *Id.*

7. Synthon noted that in light of Fleischhacker, a "worker skilled in the art would have immediately envisaged administering memantine by an oral route" for at least the following reasons (1) "oral administration is the most common, natural route of administration, especially for a long term disease condition"; (2) "memantine was already commercially sold as an oral tablet in Europe for treating related symptoms"; and (3) "the genus of possible routes of administration is limited to a few routes." *Id.* Synthon also

[3] Orchid's Notice Letter at FRX-AT-03169270-273.

[4] Interpharm's Notice Letter at FRX-AT-03490316-317; *see also* Synthon's Notice Letter at FRX-AT-03169538-539.

acknowledged the "enormous range" claimed and noted that "[b]ecause all reasonable pharmaceutical dose amounts are included (along with many unreasonable dose amounts), the worker of ordinary skill in the art could have been in possession of a method where the amount of memantine administered was within the claimed range." *Id.*

8. With respect to anticipation under § 102, Interpharm argued:

> [g]iven that memantine was found to improve loss of memory in psychogeriatric patients and memory loss was known to be the most characteristic clinical feature of Alzheimer's disease, it [was] the 'natural result flowing from the operation as taught' that memantine was used for the treatment of Alzheimer's disease prior to the '703 Patent and thus an anticipation of the '703 Patent claims.

Interpharm's Notice Letter at FRX-AT-03490317 (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)).

D. Invalidity: § 103 – Obviousness

9. Numerous generic manufacturers argued that the '703 patent was invalid for obviousness under § 103[5].

10. With respect to obviousness, Mylan argued that the claims were obvious over the prior art if theywere read to cover the use of the administration of memantine to "Alzheimer's disease patients to ameliorate one or more symptoms associated with the disease, such as an improvement in the patients' cognitive function or day to day function." Mylan's Notice Letter at FRX-AT-03490165. Specifically, Mylan argued that if the claims of the '703 reexamination were "Construed to Cover Prevention or Treatment of Moderate to Severe Dementia of the Alzheimer's Type," then the claims were obvious over the following references (either individually or in combination):

    1. Japanese Publication No. JP-58-4718;

    2. Rote Liste 63 008 (1986);

    3. Marcea et al., *Therapiewoche*, 38: 3097-3100 (1988);

[5] Cobalt's Notice Letter at FRX-AT-03490271-275; *see also* Lupin's Notice Letter at FRX-AT-03490128-130; *see also* Teva's Notice Letter at FRX-AT-03488156-161;*see also* Wockhardt's Notice Letter at FRX-AT-03490225-231; *see also* Dr. Reddy's Notice Letter at FRX-AT-03490061-068; *see also* Genpharm's Notice Letter at FRX-AT-03490092-100; *see also* Interpharm's Notice Letter at FRX-AT-03490308-316; *see also* Mylan's Notice Letter at FRX-AT-03490164-172; *see also* Synthon's Notice Letter at FRX-AT-03169539-540; *see also* Apotex's Notice Letter at FRX-AT-03169556-557; *see also* Ranbaxy's Notice Letter at FRX-AT-03483939-942; *see also* Orchid's Notice Letter at FRX-AT-03169263-270.

4. Ambrozi et al., *Pharmacopsychiatry*, 21:144-146 (1988); and

5. Fleishhacker et al., Progress in Neuro-Psychopharmacology and Biological Psychiatry, 10:87-93 (1986).

See id. at FRX-AT-03490167.

12. Mylan reasoned that "[i]t is sufficient that Marcea provides a reason to use memantine in the treatment of Alzheimer's disease," *id.* at FRX-AT-03490169; that "[i]t is sufficient that Ambrozi provide[s] a reason for the use of memantine for the prevention or treatment of Alzheimer's disease," *id.* at FRX-AT-03490170; and that "Fleishhacker suggests the use of memantine for less severe (e.g., moderately severe) forms of Alzheimer's disease." *Id.* at FRX-AT-03490171.

13. Mylan also argued that if the claims of the '703 reexamination were "Construed to Cover Prevention or Treatment of Cerebral Ischemia or Treatment of an Imbalance of Neuronal Stimulation," then the claims were obvious over the following references (either individually or in combination):

1. Gill et al., *Journal of Neuroscience*, 7(10):3343-49 (1987);

2. Olney et al., *European Journal of Pharmacology*, 142:319-30 (1987);

3. Fisher et al., *Arzneimittelforschung*, 27(7): 1487-89 (1977);

4. Henkel et al., *J. Med. Chem.*, 25:51-56 (1982); and

5. Schneider et al., *Deutsch. Med. Wochenschr.*, 109:987-90 (1984).

Id. at FRX-AT-03490171-172.

14. With respect to those references, Mylan argued (1) "Gill et al. established that NMDA receptors are involved in the mechanism of ischemia-induced neuronal degeneration"; (2) "Olney et al. established that a common property of anti-parkinsonian agents is to act as NMDA antagonists"; and "[t]hus, since memantine exhibited anti-parkinsonian activity (Fisher etc.), it would have been obvious to conclude that memantine could penetrate the blood-brain barrier and function as an NMDA receptor antagonist, treating or preventing cerebral ischemia/an imbalance of neuronal stimulation." *Id.* at FRX-AT-03490172.

E. Invalidity: § 112 – Enablement

15. Numerous Generic Companies argued that the '703 patent was invalid under § 112 for lack of enablement[6].

16. With respect to § 112 enablement, Mylan argued that the '703 patent failed to provide "any example in which adamantane derivatives [were] used to treat a patient diagnosed with Alzheimer's disease, either by preventing or treating cerebral ischemia, treating an imbalance of neuronal stimulation, or preventing or treating Alzheimer's disease per se." Mylan's Notice Letter at FRX-AT-03490161.

17. Mylan also argued that the '703 patent was not enabled because based on the dose range disclosed (1 to 10,000 times), the "teachings of the '703 patent are, at best, 'in the category of an invitation to experiment in order to determine how to make use of' the patentee's discovery of the NMDA-receptor antagonistic activity of certain adamantane derivatives." *Id.* (quoting *In re Gardner*, 427 F.2d 786 (C.C.P.A. 1970).

18. Mylan further argued, citing to *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318 (Fed. Cir. 2005), that the '703 patent was not enabled because it "discloses that certain compounds (memantine and other adamantine derivatives) exhibit a particular pharmacological activity (NMDA receptor antagonism) without demonstrating that those compounds actually are effective in treating patients (those diagnosed with Alzheimer's disease)" and that "at the time of the '703 application, those skilled in the art would not have concluded that NMDA receptor antagonists would be effective in treating Alzheimer's disease." *Id.*

19. Mylan also argued that "[t]he non-enabling nature of the '703 patent becomes clearer when viewed using the factors set forth in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988)." *Id.* at FRX-AT-03490162.

F. Invalidity: § 112 – Written Description

20. Numerous Generic Companies argued that the '703 patent was invalid under § 112 for lack of written description[7].

---

[6] Cobalt's Notice Letter at FRX-AT-03490276-277; *see also* Teva's Notice Letter at FRX-AT-03488162-163; *see also* Upsher-Smith's Notice Letter at FRX-AT-03169291-294; *see also* Wockhardt's Notice Letter at FRX-AT-03490220-225; *see also* Genpharm's Notice Letter at FRX-AT-03490088-093; *see also* Mylan's Notice Letter at FRX-AT-03490156-164; *see also* Orchid's Notice Letter at FRX-AT-03169270-273.

[7] Cobalt's Notice Letter at FRX-AT-03490275-276; *see also* Genpharm's Notice Letter at FRX-AT-03490080-084; *see also* Mylan's Notice Letter at FRX-AT-03490152-156; *see also* Apotex's Notice Letter at FRX-AT-03169557.

21. With respect to § 112 written description, Mylan argued, that if the claims "require prevention or treatment of cerebral ischemia or of 'an imbalance of neuronal stimulation after Alzheimer's disease,'" then the claims do not satisfy § 112 written description because "the treatment of cerebral ischemia in humans has eluded researchers for decades, and in fact still eludes them." Mylan's Notice Letter at FRX-AT-03490152-153.

22. Mylan argued further that if the claims "were construed to be directed to the use of certain adamantine derivatives to treat moderate to severe dementia of the Alzheimer's type per se," they would fail the § 112 written description requirement because at the time of the reexamination, "NMDA receptor antagonists were contraindicated for use in treating Alzheimer's disease" and "the '703 patent does not provide any positive disclosure that would refute th[at] understanding." *Id.* at FRX-AT-03490153-156.

G. Invalidity: Patent Term Extension

23. At least one Generic Company argued that "[a]ll claims of the '703 patent directed to memantine are unenforceable at least past April 11, 2010." Cobalt's Notice Letter at FRX-AT-03490277.

24. Specifically, Cobalt asserted that the claims of the '703 patent that were the subject of the patent term extension could not "be enforced owing to their surrender during reexamination proceedings." *Id.* (citing 35 U.S.C. § 307; MPEP § 2293; *Fortel Corp. v. Phone-Mate, Inc.*, 825 F.2d 1577, 1580–81 (Fed. Cir. 1987).

25. Moreover, Cobalt argued that because "the claims that issued pursuant to the reexamination proceeding were not part of the original patent term extension as-filed . . . [those] claims of the '703 patent [could not] be enforced past April 11, 2010, even if the PTO grant[ed] the patent term extension." *Id.*

H. Invalidity: § 305 – Impermissible Claim Broadening During Reexamination

26. Several Generic Companies argued that claims 17-19 of the '703 patent were broadened during reexamination, and were thus invalid[8].

27. Upsher-Smith noted that "[c]laims 17 through 19 were added during reexamination proceedings"; that "[a]s compared with the previously issued claims of the '703 patent, the added claims replace[d] the language 'method for the prevention or treatment of cerebral ischemia' with the language 'method for the treatment of an imbalance of neuronal stimulation"; and that "[a]s a consequence, the added claims are more broad in

[8] Barr's Notice Letter at FRX-AT-02588346; *see also* Upsher-Smith's Notice Letter at FRX-AT-03169294-295; *see also* Wockhardt's Notice Letter at FRX-AT-03490218-220.

at least one respect than the originally issued claims, and are therefore invalid." Upsher-Smith's Notice Letter at FRX-AT-03169294.

28. Specifically, Upsher-Smith argued that claim 17 was broadened under either the test articulated in *Thermalloy v. Aavid Eng'g, Inc.*, 121 F.3d 691 (Fed. Cir. 1997), in which the Federal Circuit reasoned that a claim is enlarged "if it includes within its scope any subject matter that would not have infringed the original patent," 121 F.3d 691, 692 (Fed. Cir. 1995), or under the standard as articulated in *Quantum Corp. v. Rodime, PLC*, , in which the Federal Circuit reasoned that "[a] claim that is broader in any respect is considered to be broader than the original claims even though it may be narrower in other respects." 65 F.3d 1577, 1580 (Fed. Cir. 1995). With respect to the *Thermalloy* test, Upsher-Smith argued that claim 17 was broadened because the claim would cover "treatment of an imbalance of neuronal stimulation related to cerebral ischemia as in the original claim 1 . . . but . . . would also cover imbalances of neuronal stimulation that are not related to cerebral ischemia." Upsher-Smith's Notice Letter at FRX-AT-03169295.

29. With respect to the *Quantum Corp.* test, Upsher-Smith reasoned that "claim 17 is more broad than claim 1 in at least one specific respect, which is that the phrase 'treatment of an imbalance of neuronal stimulation' encompasses subject-matter that is not either 'prevention' or 'treatment' of 'cerebral ischemia'" and thus, "claim 17 [was] invalid as impermissibly broadened during reexamination." *Id.*; *see also* Wockhardt's Notice Letter at FRX-AT-03490218-220 (providing similar reasoning).

EXHIBIT K

Markman Claim Construction Summary

Term	Claim(s)	Court's Construction
Cerebral ischemia*	1, 14	an imbalance of neuronal stimulation mechanisms
Prevention of cerebral ischemia*	1	prevention of an imbalance of neuronal stimulation mechanisms
Treatment of cerebral ischemia*	1, 14	an antagonistic intervention with regard to the N–methyl–D–aspartate [NMDA] receptor channels
Imbalance of neuronal stimulation after Alzheimer's disease	17	a pathophysiological situation characterized by an excessive inflow of calcium through the NMDA receptor channels after Alzheimer's disease
Alzheimer's disease	1, 10, 14, 17	dementia of the Alzheimer's type, as characterized by accepted diagnostic criteria, such as those set forth in the Diagnostic and Statistical Manual of Mental Disorders, version III–R, and further characterized by the presence of neuritic plaques and neurofibrillary tangles in the brain
Patient diagnosed with Alzheimer's disease	1, 14, 17	a live person diagnosed with dementia of the Alzheimer's type, as characterized by accepted diagnostic criteria, such as those set forth in the Diagnostic and Statistical Manual of Mental Disorders, version III–R
Treatment of imbalance of neuronal stimulation after Alzheimer's disease*	17	an antagonistic intervention with regard to the excessive inflow of calcium through NMDA receptor channels after Alzheimer's disease
Treatment of Alzheimer's disease*	10	Plain and ordinary meaning, incorporating by reference the court's construction of Alzheimer's disease
Effective amount	1, 14, 17	an amount shown to cause improvement, in comparison to placebo
Effective cerebral ischemia-alleviating or preventive amount	11	an amount shown to treat or eliminate an imbalance of neuronal stimulation, in comparison to placebo treatment
Amount effective to prevent degeneration and loss of nerve cells after ischemia	13	an amount shown to eliminate degeneration and loss of nerve cells after an acute interruption of blood supply
Patient . . . in need thereof	1, 14	Plain and ordinary meaning
Patient . . . in need of such treatment	17	Plain and ordinary meaning

*Magistrate Judge's construction challenged by Defendants.

EXHIBIT L

Namenda Litigation Timeline – Key Events Summary

Date	Event
Jan. 10, 2008	Complaint Filed
June 2, 2008	Consolidation Order (Case Nos. 08-22, 08-52, and 08-291)
June 16, 2008	Consolidation Order (Case No. 08-336)
July 8, 2008	Scheduling Order Entered
November 12, 2008	Technology Tutorial
December 15, 2008	*Markman* Hearing
March 9, 2009	Report and Recommendation to Transfer Orgenus and Orchid to DNJ
May 8, 2009	Stipulation of Dismissal as to Barr
July 2, 2009	Claim Construction Report and Recommendation by Magistrate Judge
August 27, 2009	Order Transferring Orgenus and Orchid to NJ
September 2, 2009	Stipulation of Dismissal as to Amneal
September 8, 2009	Stipulation of Dismissal as to Upsher-Smith
September 9, 2009	Stipulation of Dismissal as to Apotex
September 10, 2009	Stipulation of Dismissal as to Wockhardt
October 8, 2009	Stipulation of Dismissal as to Genpharm
October 9, 2009	Stipulation of Dismissal as to Sun Pharma
October 19, 2009	Stipulation of Dismissal as to Cobalt
October 20, 2009	Fact Discovery Close
November 5, 2009	Stipulation of Dismissal as to Teva
November 16, 2009	Stay as to Dr. Reddy's
November 20, 2009	Opening Expert Reports
December 14, 2009	Stipulation of Dismissal as to Dr. Reddy's
December 14, 2009	Stay as to Lupin
December 18, 2009	Rebuttal Expert Reports
January 22, 2010	Expert Discovery Close
February 11, 2010	Stipulation of Dismissal as to Lupin
February 26, 2010	Proposed Pretrial Order Filed
March 15, 2010	Agreement-In-Principle reached between Forest and Merz and Mylan
April 5, 2010	Scheduled date for trial to begin (note: Trial did not occur.)
July 22, 2010	Stay as to Mylan
August 26, 2010	Stipulation of Dismissal as to Mylan

EXHIBIT M

TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

Page

LEGAL UNDERSTANDING AND STANDARD

1. Based upon my review of the case law and the facts of the present litigation, it is my understanding that some or all of the following legal rules, standards, and requirements apply.

I. Infringement under the Hatch-Waxman Act

2. Under 35 U.S.C. § 271(e)(2):

> [i]t shall be an act of infringement to submit—(A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent.

3. Courts have interpreted § 271(e)(2)(A) as creating an artificial act of infringement that establishes case or controversy jurisdiction, but "[o]nce jurisdiction is established . . . the substantive determination whether actual infringement or inducement will take place is determined by traditional patent infringement analysis . . . ." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003).

4. As in all patent litigations, the patent holder in a Hatch-Waxman case has the burden of proving infringement by a "preponderance of the evidence." *Warner-Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1341 n.15 (Fed. Cir. 2005).

II. Claim Construction

A. Two-Step Process

5. Before infringement of a claim can be appropriately considered, the Federal Circuit requires completion of a claim construction process. This process normally occurs at a hearing (*i.e.*, a *Markman* Claim Construction Hearing). *See Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996). A determination of patent infringement is a two-step process.

6. First, the claims must be construed to determine scope and meaning. In other words, the claim language is reviewed to determine what the words in the claim mean. *PC Connector Sols. LLC v. SmartDisk Corp.*, 406 F.3d 1359, 1362 (Fed. Cir. 2005). Claim construction necessarily precedes a determination of whether the claims read on an accused product for infringement purposes. *Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1562 (Fed. Cir. 1990); *see also SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 882 (Fed. Cir. 1988).

7. Claim construction is a matter of law "exclusively within the province of the court." *Markman*, 517 U.S. at 372; *see also Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1304 (Fed. Cir. 1999) (noting that claim construction "is a question of law" that is reviewed de novo); *see also Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1453 (Fed. Cir. 1998) (*en banc*).

8. A claim is interpreted as it would be by a person skilled in the art in light of the prior art, the specification, the other claims, and the prosecution history of the patent. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *see also Specialty Composites v. Cabor Corp.*, 845 F.2d 981, 986 (Fed. Cir. 1988).

9. In *Phillips v. AWH Corp.*, the Federal Circuit clarified the methodology to be used to interpret disputed claim terms. The court stated that claim terms are generally given their "ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in questions at the time of the invention." 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (*en banc*). The interpretation of the scope of a claim term, therefore, begins with an inquiry of how a person of ordinary skill in the art understands the term. *Id.* at 1313. This inquiry cannot, however, merely consider the ordinary meaning of a claim term in a vacuum – the term must be read in the context of the intrinsic evidence (*i.e.*, the claim itself, the written description, and the prosecution history). *Id.* at 1313–14.

10. Thus, the starting point for the claim interpretation process is the intrinsic evidence. *Id.* at 1314. In the review of intrinsic evidence, the specification is usually dispositive; "it is the single best guide to the meaning of a disputed term." *Id.* at 1315 (citation omitted). The claims of the patent also serve to introduce context as to the meaning of the claim term. *Id.* at 1314–15. Additionally, the prosecution history, if in evidence, can be used to demonstrate how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution. *Id.* at 1317. The prosecution history can make the claim scope narrower than it would otherwise be. *Id.*

11. Furthermore, "extrinsic evidence, which 'consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries and learned treaties,'" may also be considered to determine the meaning of a claim term. *Id.* at 1317 (quoting *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 980 (Fed. Cir. 1995), *aff'd* 517 U.S. 370). Although extrinsic evidence is, in general, "less reliable than the patent and its prosecution history in determining how to read claim terms," *id.* at 1318, it can also be useful in interpretation of claim terms. *Id.* at 1317. Importantly, however,

extrinsic evidence "is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence." *Id.* at 1319.

12. Additionally, "[t]he sequence of steps used by the judge in consulting various sources is not important; what matters is for the court to attach the appropriate weight to be assigned to those sources in light of the statutes and policies that inform patent law." *Id.* at 1324.

13. Second, the properly construed claims are compared against the accused product or method. This comparison is considered a question of fact. *Cybor Corp.*, 138 F.3d at 1454; *see also Warner-Lambert Co.*, 418 F.3d at 1340. In other words, a fact-finding determination is made as to whether the claims cover the accused products or methods. *Johnson Worldwide Assocs. v. Zebco Corp.*, 175 F.3d 985, 988 (Fed. Cir. 1999).

14. Infringement is proven when the patent holder shows by a preponderance of the evidence that the accused product or method meets each claim limitation, as construed, literally or by the doctrine of equivalents. *Deering Precision Instruments, L.L.C. v. Vector Distrib. Sys.*, 347 F.3d 1314, 1324 (Fed. Cir. 2003); *see also Dolly, Inc. v. Spalding & Evenflo Cos.*, 16 F.3d 394, 397 (Fed. Cir. 1994).

B. Person of Ordinary Skill in the Art

15. "[H]ow a person of ordinary skill in the art understands a claim term" is the "baseline" from which claim interpretation begins. *Phillips*, 415 F.3d at 1313. There is a "well-settled understanding" that "inventors are typically persons skilled in the field of the invention and that patents are addressed to and intended to be read by others of skill in the pertinent art." *Id.* Courts consider a number of factors in determining the level of skill in the art including: "'(1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field.'" *Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007) (quoting *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 696 (Fed. Cir. 1983)).

III. Infringement Defenses

A. Preponderance of Evidence – Standard

16. "A claim for patent infringement must be proven by a preponderance of the evidence, . . . which simply requires proving that infringement was more likely than not to have

occurred." *Warner-Lambert Co.*, 418 F.3d at 1341 n.15 (internal citation omitted). Under this standard, "a patentee must supply sufficient evidence to prove that the accused product or process contains, either literally or under the doctrine of equivalents, every limitation of the properly construed claim." *Seal-Flex, Inc. v. Athletic Track & Court Constr.*, 172 F.3d 836, 842 (Fed. Cir. 1999); *see also, Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995).

B. Direct Infringement

17. The protection afforded to a U.S. patent holder is defined by the claims of the patent. "It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled to the right to exclude.'" *Phillips*, 415 F.3d at 1312 (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004)). Section 271, defines patent infringement as "whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent . . . ." 35 U.S.C. § 271(a).

18. Thus, infringement is measured against the "patented invention," *i.e.,* the patent claims. For infringement, every limitation that is present in a patent claim must be found in an accused product or method, exactly or by a substantial equivalent. *Mas-Hamilton Grp. v. LaGard, Inc.*, 156 F.3d 1206, 1211 (Fed. Cir. 1998). "If even one limitation is missing or not met as claimed, there is no literal infringement." *Id.*

1. Literal Infringement

19. To demonstrate literal infringement, a patent holder must prove by a preponderance of the evidence that the allegedly infringing product or method embodies every element of the asserted claims. *Townsend Eng'g Co. v. Hitec Co.*, 829 F.2d 1086, 1090 (Fed. Cir. 1987). This conclusion follows from the principle that "[e]ach element contained in a patent claim is deemed material to defining the scope of the patented invention[.]" *Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29 (1997); *see also Lemelson v. United States,* 752 F.2d 1538, 1551 (Fed. Cir. 1985); *see also Bristol-Myers Squibb Co. v. Andrx Pharms., Inc.*, 343 F. Supp. 2d 1124, 1146 (S.D. Fla. 2004).

20. As to infringement of dependent claims (*i.e.*, those that reference another claim), "[i]t is axiomatic that dependent claims cannot be found infringed unless the claims from which they depend have been found to have been infringed. *Wahpeton Canvas Co., Inc. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). This axiom follows because a

dependent claim incorporates each of the limitations of the claims from which it depends. *See Kim v. ConAgra Foods, Inc.*, 465 F.3d 1312, 1316 n.1 (Fed. Cir. 2006) (holding that, "[s]ince we conclude that [the independent claim] is not infringed, it necessarily follows that the dependent claims are also not infringed").

2. Infringement under the Doctrine of Equivalents

21. Even if a patent holder cannot demonstrate literal infringement, under certain circumstances, infringement may be established under the "doctrine of equivalents." Under this doctrine, a product or method that does not literally infringe a patent claim may be found to infringe "if there is 'equivalence' between the elements of the accused product or method and the claim limitations of the patented invention." *Warner-Jenkinson Co.*, 520 U.S. at 21 (citing *Graver Tank & Mfg. Co.*, 339 U.S. at 609); *see also Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 726 (2002).

22. "Equivalence" between an element present in the accused device or method and a claim limitation is established when "'insubstantial differences'" are present. *Sage Prods. Inc. v. Devon Indus., Inc.*, 126 F.3d 1420, 1423 (Fed. Cir. 1997) (quoting *Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1517–18 (Fed. Cir. 1995) (*en banc*), *rev'd on other grounds*, 520 U.S. 17 (1997)). It remains the patent holder's burden to show under the preponderance of the evidence standard that any changes made by an accused infringer are "insubstantial." *See Ciba Vision Corp. v. Alcon Labs., Inc.*, No. 97-0626, 1997 WL 667942, at *3 (N.D. Tex. Oct. 21, 1997) (where the patent holder failed to show how use of certain stabilizers were only a minor or insubstantial change from using EDTA or trometamol, a finding of infringement would "give the doctrine of equivalents such broad play so as to effectively eliminate the EDTA and trometamol [claim] elements in their entirety").

23. The doctrine of equivalents is an equitable doctrine. Its purpose is to prevent turning of a patent into a "hollow and useless thing" if the patent holder were held to the precise claim language used in the patent. *See Graver Tank & Mfg. Co.*, 339 U.S. at 607. As a result, "[a]pplication of the doctrine of equivalents is the exception . . . not the rule." *Wallace London & Clemco Prods., Inc. v. Carson Pirie Scott & Co.*, 946 F.2d 1534, 1538 (Fed. Cir. 1991).

C. Indirect Infringement

24. Indirect infringement, either inducement to infringe under 35 U.S.C. § 271(b) or contributory infringement under 35 U.S.C. § 271(c), "can only arise in the presence of

direct infringement." *Dynacore Holdings Corp. v. U.S. Philips Corp.*, 363 F.3d 1263, 1272 (Fed. Cir. 2004). The direct infringer however, "is typically someone other than the defendant accused of indirect infringement." *Id.*

1. Induced Infringement

25. Section 271(b) provides that "[w]hoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). To prevail on a claim for inducement pursuant to § 271(b), "'the patentee must establish 'first that there has been direct infringement, and second that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement.'" *ACCO Brands, Inc. v. ABA Locks Mfrs. Co.*, 501 F.3d 1307, 1312 (Fed. Cir. 2007) (quoting *Minn. Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1304–05 (Fed. Cir. 2002)).

26. The Federal Circuit has advised that "[s]pecific intent requires a 'showing that the alleged infringer's actions induced infringing acts and that he knew or should have known his actions would induce actual infringements.'" *Id.* (quoting *DSU Med. Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1304 (Fed. Cir. 2006) (*en banc* in relevant part) (quoting *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 554 (Fed. Cir. 1990))).

2. Contributory Infringement

27. "Contributory infringement prohibits the importation into the United States of a component or apparatus for use in a patented process that has no use except through practice of the patented method." *Alloc, Inc. v. Int'l Trade Cmm'n*, 342 F.3d 1361, 1374 (Fed. Cir. 2003). Section 271 provides:

> [w]hoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.

28. 35 U.S.C. § 271(c). "Section 271(c) 'require[s] a showing that the alleged contributory infringer knew that the combination for which his component was especially designed was both patented and infringing.'" *Trell v. Marlee Elecs. Corp.*, 912 F.2d 1443, 1447 (Fed. Cir. 1990) (quoting *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 377 U.S. 476, 488 (1964)).

IV. Invalidity Defenses

A. Clear and Convincing – Standard

29. A patent is "presumed valid." 35 U.S.C. § 282. The presumption of validity applies independently to each claim of a patent. *Id.*

30. A party challenging the validity of a patent or any of its claims bears the burden of introducing "clear and convincing evidence" establishing invalidity. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376 (Fed. Cir. 1986); *see also Lindemann Maschinenfabrik GmbH v. Am. Hoist & Derrick Co.*, 730 F.2d 1452, 1459 (Fed. Cir. 1984). The clear and convincing standard is an intermediate standard which lies somewhere between "beyond a reasonable doubt" and a "preponderance of the evidence." This standard is a stricter requirement than the "preponderance of the evidence" standard as described above, *see* Exhibit M, Paragraph 16, the latter of which means that the party bearing the burden must show merely that it is more likely than not that the assertion is true.

31. The clear and convincing standard "has been described as evidence which produces in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions [is] highly probable." *Janssen Pharmaceutica N.V. v. Mylan Pharms., Inc.*, 456 F. Supp. 2d 644, 652 (D.N.J. 2006) (quoting *Buildex, Inc. v. Kason Indus., Inc.*, 849 F.2d 1461, 1463 (Fed. Cir. 1988)) (internal quotation omitted); *see also Price v. Symsek*, 988 F.2d 1187, 1191 (Fed. Cir. 1993).

32. The Federal Circuit has stated, however, that it is more difficult to invalidate a patent based on prior art that was previously considered by the USPTO during prosecution. *See, e.g., EWP Corp. v. Reliance Universal, Inc.*, 755 F.2d 898, 905 (Fed. Cir. 1985) (noting that a party's "burden of proof under 35 U.S.C. § 282 is more easily carried" where the court had "no PTO view before [it] on obviousness in view of [certain] references"); *see also Jurgens v. McKasy*, 927 F.2d 1552, 1558 (Fed. Cir. 1991) ("[o]ne *may* invalidate a patent more easily with prior art not considered by the examiner."); *see also Kaufman Co. v. Lantech, Inc.*, 807 F.2d 970, 973 (Fed. Cir. 1986); *see also Schering Corp. v. Precision-Cosmet Co.*, 614 F. Supp. 1368, 1371 (D. Del. 1985).

B. Prior Art

33. To be used to invalidate a patent claim, a patent or other publication must first qualify as "prior art." *See* 35 U.S.C. §§ 102 , 103. In other words, prior art can be used to invalidate a patent claim as being anticipated or as being obvious. *See* 35 U.S.C. §§ 102, 103.

"'[P]rior art' in legal theory . . . is knowledge that is available, including what would be obvious from it, at a given time, to a person of ordinary skill in an art." *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1453 (Fed. Cir. 1984).

34. Prior art includes inventions that were "known or used by others in [the United States], or patented or described in a printed publication in [the United States] or a foreign country, before the invention thereof by the applicant for patent." 35 U.S.C. § 102(a). Prior art also includes inventions that were "patented or described in a printed publication in [the United States] or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b). Printed publications include articles in non-patent literature. *See Novo Nordisk Pharmaceuticals, Inc. v. Bio-Tech. Gen. Corp.*, 424 F.3d 1347, 1355–56 (Fed. Cir. 2005).

C. Anticipation – 35 U.S.C. § 102

35. A claim is invalid for anticipation under 35 U.S.C. § 102 if "a single prior art reference discloses each and every limitation of the claimed invention." *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). "Invalidity based on 'anticipation' requires that the invention is not in fact new . . . . [a] single reference must describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art." *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002); *see also Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1267 (Fed. Cir. 1991) (noting "[a]nticipation under § 102(a) requires that the identical invention that is claimed was previously known to others and thus is not new"). Thus, each and every element of a claim, as properly construed, must be found either explicitly or inherently in a single prior art reference. *See Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008).

36. A patent claim however, "'cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled.'" *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research,* 346 F.3d 1051, 1054 (Fed.Cir.2003) (quoting *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003)). Furthermore, a prior art reference need not demonstrate utility in order to serve as an anticipating reference under section 102. In *In re Hafner*, the court stated that "a disclosure lacking a teaching of how to use a fully disclosed compound for a specific, substantial utility or of how to use for such purpose a compound produced by a fully disclosed process is . . . entirely adequate to anticipate a claim to either the product or the

process and, at the same time, entirely inadequate to support the allowance of such a claim [under 35 U.S.C. § 112]." 410 F.2d 1403, 1405 (C.C.P.A. 1969)[1].

37. For anticipation, non-analogous or analogous prior art may be used. The question of whether a reference is analogous art is not relevant to whether that reference anticipates under 35 U.S.C. § 102, as "[a] reference may be from an entirely different field of endeavor than that of the claimed invention or may be directed to an entirely different problem from the one addressed by the inventor, yet the reference will still anticipate if it explicitly or inherently discloses every limitation recited in the claims." *In re Schreiber*, 128 F.3d 1473, 1478 (Fed. Cir. 1997); *see also In re Self*, 671 F.2d 1344, 1350 (C.C.P.A. 1982).

38. "Anticipation can occur when a claimed limitation is 'inherent' or otherwise implicit in the relevant reference." *Standard Havens Prods., Inc. v. Gencor Indus., Inc.*, 953 F.2d 1360, 1369 (Fed. Cir. 1991) (noting that "[a]n anticipatory reference . . . need not duplicate word for word what is in the claims"). The Federal Circuit has reasoned that inherency can be established when "prior art necessarily functions in accordance with, or includes, the claimed limitations." *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed.Cir.2002). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981).

39. Moreover, "[i]nherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure." *Abbott Labs. v. Baxter Pharma. Prods. Inc.*, 471 F.3d 1363, 1367–68 (Fed. Cir. 2006) (noting "[o]ur cases have consistently held that a reference may anticipate even when the relevant properties of the thing disclosed were not appreciated at the time"); *see also Atlas Power Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) (noting "[i]nherency is not necessarily conterminous with the knowledge of those of ordinary skill in the art"). In *Atlas*, the Federal Circuit reasoned that:

> [a]rtisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. However, the

[1] *See also In re Schoenwald*, 964 F.2d 1122, 1124 (Fed. Cir. 1992); *see also In re Samour*, 571 F.2d 559, 563–64 (C.C.P.A. 1978); *see also In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349–52 (Fed.Cir.2002) (finding anticipation where applicant sought a patent based on a new use for a previously disclosed method); *see also In re Donohue*, 632 F.2d 123, 126 n. 6 (C.C.P.A. 1980) (*citing In re Samour*, 571 F.2d at 563–64) (noting that "proof of utility is not a prerequisite to availability of a prior art reference under 35 U.S.C. § 102(b)"); *see also Application of Lukach*, 442 F.2d 967, 969 (C.C.P.A. 1971) (recognizing that there are "anomalies between the requirements for claim-anticipating disclosures and for claim-supporting disclosures").

> discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.

190 F.3d at 1347.

D. Obviousness – 35 U.S.C. § 103

40. Under 35 U.S.C. § 103:

> A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

See also King Pharm., Inc. v. Eon Labs, Inc., 616 F.3d 1267, 1274 (Fed. Cir. 2010).

1. Obviousness Analysis

41. An obviousness analysis should be based on: 1) the scope and content of the prior art; 2) the differences between the prior art and the claim; 3) the level of ordinary skill in the art at the relevant time; and 4) and any objective evidence (*i.e.,* secondary considerations or indicia) of non-obviousness, to the extent they exist. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 399 (2007); *see also Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

42. Rationales for finding a claim to be obvious include: 1) "[c]ombining prior art elements according to known methods to yield predictable results"; 2) "[s]imple substitution of one known element for another to obtain predictable results"; 3) use of known techniques to improve similar devices, methods, or products in the same way; 4) applying a known technique to known devices, methods, or products ready for improvement to yield predictable results; 5) "'[o]bvious to try' - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success"; 6) "[k]nown work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art"; and 7) "[s]ome teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention." *Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR Int'l Co. v. Teleflex Inc.: III. Rationales To Support Rejections Under 35 U.S.C. § 103*, 72 Fed. Reg. 57526, 57528–534 (Oct. 10, 2007).

43. It is impermissible, however, to engage in hindsight reconstruction of the claimed invention, using the applicant's invention as a template and selecting elements from the prior art to fill the gaps. *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). "[R]ejection on obviousness grounds cannot be sustained by mere conclusory statements; instead there must some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.*

2. Analogous Art

44. A combination of two or more references can render a claim invalid as obvious whether or not there is an explicit suggestion in one of the references to combine the two references, if as a matter of skill or practice in the field, it would be known to do so. *In re Nilssen,* 851 F.2d 1401, 1403 (Fed. Cir. 1988).

45. For a reference to be used properly in an obviousness rejection under § 103, the reference must be analogous art to the claimed invention. *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). Analogous art does not require that the reference be from the same field of endeavor as the claimed invention. "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one." *KSR Int'l Co.*, 550 U.S. at 417.

46. Rather, a reference is analogous art to the claimed invention if: 1) the reference is from the same field of endeavor as the claimed invention (even if it addresses a different problem); or 2) the reference is reasonably pertinent to the problem faced by the inventor (even if it is not in the same field of endeavor as the claimed invention). *Bigio*, 381 F.3d at 1325.

47. For a reference to be "reasonably pertinent" to the problem, it must "logically [] have commended itself to an inventor's attention in considering his problem." *In re Icon Health & Fitness, Inc.*, 496 F.3d 1374, 1379–80 (Fed. Cir. 2007) (quoting *In re Clay*, 966 F.2d 656, 658 (Fed. Cir. 1992)). "If a reference disclosure has the same purpose as the claimed invention, the reference relates to the same problem, and that fact supports use of that reference in an obviousness rejection[,] [a]n inventor may well have been motivated to consider the reference when making his invention." *In re Clay*, 966 F.2d at 659.

48. It is, thus, necessary to assess the interrelated teachings of prior art patents as well as the background knowledge of the ordinarily skilled person in order to determine an apparent reason to combine the disclosures in various references. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to

combine the elements in a way the claimed new invention does." *KSR Int'l Co.*, 550 U.S. at 418.

3. Secondary Considerations

49. An obviousness analysis must consider any objective evidence (*i.e.,* secondary considerations or indicia) of non-obviousness, to the extent they exist. *KSR Int'l Co.*, 550 U.S. at 399; *see also Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 667–68 (Fed. Cir. 2000); *see also Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 957 (Fed. Cir. 1997); *see also Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 991 (Fed. Cir. 1988).

50. Thus, an inquiry pertinent to secondary indicia of non-obviousness should consider evidence, if available, regarding any of the following:

- Any **long-felt unmet need** in the art that was satisfied by the invention of the patent
- Any **failure of others** to achieve the results of the invention;
- Any **commercial success** or lack thereof of the products and processes covered by the invention;
- Any deliberate **copying** of the invention by others in the field;
- Any taking of **license** under the patent by others;
- Whether the invention was contrary to the accepted wisdom of the prior art (*i.e.*, **teaches away**);
- Any expression of **disbelief or skepticism** by those skilled in the art upon learning of the invention;
- Any **unexpected results** achieved by the invention;
- Any **praise of the invention** by others skilled in the art; and
- Any **lack of contemporaneous and independent invention** by others.

See Federal Circuit Bar Association, *Model Patent Jury Instructions*, B.4.3 (Feb. 2010); *see also KSR Int'l Co.*, 550 U.S. at 406 (*citing Graham*, 383 U.S. at 17–18).

51. While evidence pertaining to secondary considerations must be taken into account whenever present it, however, does not necessarily control the obviousness conclusion. Accordingly, each case should be evaluated individually based on the totality of the

circumstances. *See, e.g.*, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007) ("the record establishe[d] such a strong case of obviousness that . . . alleged unexpectedly superior results [were] ultimately insufficient" to overcome an obviousness conclusion); *see also Leapfrog Enters. Inc. v. Fisher-Price Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) ("given the strength of the *prima facie* obviousness showing, the evidence on secondary considerations was inadequate to overcome a final conclusion" of obviousness); *see also Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988).

52. There also must be a nexus between any secondary indicia of non-obviousness and the claimed invention for the secondary consideration be entitled to substantial weight. *See In re Huang*, 100 F.3d 135, 139–40 (Fed. Cir. 1996). In other words, the objective evidence of non-obviousness must be attributable to the claimed invention. And, the patent holder bears the burden of establishing this nexus. *Id.; see also In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995); *see also In re Paulsen*, 30 F.3d 1475, 1482 (Fed. Cir. 1994) (reasoning that evidence of commercial success of articles not covered by the claims subject to the obviousness rejection was not probative of non-obviousness).

53. Additionally, the evidence must be reasonably commensurate in scope with the claimed invention. *See, e.g.*, *In re Kulling,* 897 F.2d 1147, 1149 (Fed. Cir. 1990); *see also In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983). However, an exemplary showing may be sufficient to establish a reasonable correlation between the showing and the entire scope of the claim, when viewed by a skilled artisan. *See, e.g.*, *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *see also In re Clemens*, 622 F.2d 1029, 1036 (C.C.P.A. 1980).

(i) Commercial Success

54. "Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." Merck & Co. Inc. v. Teva Pharma. USA, Inc., 395 F.3d 1364, 1376 (Fed. Cir. 2005). As with all secondary considerations of obviousness, there must be a nexus between the claimed invention and the commercial success. See Pro-Mold & Tool Co., Inc. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1574 (Fed. Cir. 1996) (concluding that the patentee's "lack of previous experience in the relevant market combined with its high sales of the patented product provided an inference of a nexus between its commercial success and the patented invention and are thus probative evidence of nonobviousness" as "[i]ts lack of market power in this field would seem to suggest that it was the features of the patented invention that led to the commercial success").

(ii) Unexpected Results

55. As noted above, evidence of secondary considerations may consist of a showing that a claimed compound or method possesses "unexpected properties." *In re Dillon*, 919 F.2d 688, 692–93 (Fed. Cir. 1990). A showing of unexpected results, however, must be based on evidence, not argument or speculation. *In re Mayne*, 104 F.3d 1339, 1343–44 (Fed. Cir. 1997) (conclusory statements that claimed compound possesses unusually low immune response or unexpected biological activity that is unsupported by comparative data held insufficient to overcome *prima facie* case of obviousness).

(iii) Teaches Away

56. When considering a prior art reference for purposes of conducting an obviousness analysis, a prior art reference must be considered in its entirety. In other words, the reference must be taken for everything it teaches. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 296 (Fed. Cir. 1985) (reasoning that "[a] reference . . . must have been considered for all it taught, disclosures that diverged and taught away from the invention at hand as well as disclosures that pointed towards and taught the invention at hand").

57. When considering the reference as a whole, one should consider those portions that would lead away from the claimed invention. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). However, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed . . . . " *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004); *see also* M.P.E.P. § 2123.

E. Enablement and Written Description – 35 U.S.C. § 112, First Paragraph

58. 35 U.S.C. § 112, ¶ 1 provides:

> [t]he specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

59. In *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.*, an *en banc* panel of the Federal Circuit confirmed that the written description requirement is in fact separate and distinct from the enablement requirement. 598 F.3d 1336, 1351 (Fed. Cir. 2010).

1. Enablement

60. Section 112, first paragraph, requires that a claim be enabled by the specification. 35 U.S.C. § 112, ¶ 1. The enablement requirement demands that the patent specification enable those skilled in the art to make and use the full scope of the claimed invention without undue experimentation based on the underlying facts. *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). Factors to be considered when evaluating whether there is undue experimentation include:

> 1) the quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or non-predictability of the art, and 8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

61. The "invention" that must be enabled is that defined by the particular claim or claims of the patent or patent application. *CFMT, Inc. v. YieldUP Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003). This is consistent with the general principle of patent law that the claim defines the invention for purposes of both patentability and infringement. *Curtiss-Wright Flow Control Corp. v. Velan, Inc.*, No. 04-1157, 2006 WL 6210068, at *2 (W.D. Tex. June 19, 2006).

62. "[T]he question of undue experimentation is a matter of degree." *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1253 (Fed. Cir. 2004). The Federal Circuit has described the test for undue experimentation as follows:

> [t]he test [for undue experimentation] is not merely quantitative, since considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention.

Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1360–61 (Fed. Cir. 1998) (quoting *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996)).

63. In *ALZA Corp. v. Andrix Pharmaceuticals, LLC*, the Federal Circuit affirmed a judgment of nonenablement where the specification provided "only a starting point, a direction for further research," and the patent holder "concede[d] that a person of ordinary skill in the art would have been required to engage in an iterative, trial-and-error process to practice the claimed invention even with the help of the . . . specification." 603 F.3d 935, 941 (Fed. Cir. 2010).

64. Further, the enablement requirement is linked to the utility requirement under 35 U.S.C. § 101. As noted in *Process Control Corp. v. HydReclaim Corp.*:

> [t]he enablement requirement of 35 U.S.C. § 112, ¶ 1 requires that the specification adequately discloses to one skilled in the relevant art how to make, or in the case of a process, how to carry out, the claimed invention without undue experimentation. The utility requirement of 35 U.S.C. § 101 mandates that any patentable invention be useful and, accordingly, the subject matter of the claim must be operable. If a patent claim fails to meet the utility requirement because it is not useful or operative, then it also fails to meet the how-to-use aspect of the enablement requirement.

190 F.3d 1350, 1358 (Fed. Cir.1999) (citations and footnote omitted).

65. Thus, a patent directed to a method of treating Alzheimer's disease was held invalid based on the applicant's "analytic reasoning" and guesswork drawn from the prior art. *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1326 (Fed. Cir. 2009). According to the Federal Circuit:

> [A]t the end of the day, the specification, even read in the light of the knowledge of those skilled in the art, does no more than state a hypothesis and propose testing to determine the accuracy of that hypothesis. That is not sufficient. *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325 (Fed.Cir.2005) ("If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis.").

Id. at 1327.

66. The standard for what constitutes proper enablement under 35 U.S.C. § 112 differs from the standard for what constitutes proper enablement for purposes of anticipation by a prior art reference under § 102. This is because 35 U.S.C. § 112 "provides that the specification must enable one skilled in the art to 'use' the invention whereas [section] 102 makes no such requirement as to an anticipatory disclosure." In re Hafner, 410 F.2d at 1405 (C.C.P.A. 1969).

2. Written Description

67. The statutory provision of 35 U.S.C. § 112, ¶ 1, also requires that the inventor comply with a written description requirement. *See Univ. of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 921 (Fed. Cir. 2004), *reh'g en banc denied*, 375 F.3d 1303 (Fed. Cir. 2004), *cert. denied*, 543 U.S. 1015 (2004). Specifically, in order to obtain a valid patent, the written description requirement necessitates that a patent application include a specification adequately disclosing the invention and how to make and use it. The purpose of this requirement calling for adequate disclosure guarantees that the public will receive the full benefit of the knowledge of the patent in exchange for the limited monopoly granted to the inventor. *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 150–51 (1989).

68. But, an invitation for further research cannot replace an applicant's duty to provide adequate written description of the invention. *Ariad Pharm. Inc.*, 598 F.3d at 1356. Possession of the invention is required. *Id.* at 1351.

69. The written description requirement ensures that the applicant had in his or her possession, as of the filing date of the application, the specific subject matter claimed by the applicant. *In re Wertheim*, 541 F.2d 257, 262 (C.C.P.A. 1976) (citation omitted). It requires that the applicant "place the invention in the possession of the public as fully as if the art or instrument itself had been practically and publicly employed." *Fields v. Conover*, 443 F.2d 1386, 1390 (C.C.P.A. 1971).

F. Subject Matter – Inoperability – 35 U.S.C. § 101

70. Section 101 provides that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. "If the written description fails to illuminate a credible utility, the PTO will make both a section 112, ¶ 1 rejection for failure to teach how to use the invention and a section 101 rejection for lack of utility." *In re Cortright*, 165 F.3d 1353,

1356 (Fed. Cir. 1999) (citing M.P.E.P. § 706.03(a), form ¶ 7.05.04). "This dual rejection occurs because '[t]he how to use prong of section 112 incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention.'" *Id.* (quoting *In re Ziegler,* 992 F.2d 1197, 1200 (Fed. Cir. 1993)).

71. "Thus, an applicant's failure to disclose how to use an invention may support a rejection under either section 112, ¶ 1 for lack of enablement as a result of 'the specification's . . . failure to disclose adequately to one ordinarily skilled in the art "how to use" the invention without undue experimentation,' or section 101 for lack of utility 'when there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention.'" *Id.* (quoting *Envirotech Corp. v. Al George, Inc.,* 730 F.2d 753, 762 (Fed.Cir.1984)).

G. Improperly Broadened Claims Language – 35 U.S.C. § 305

72. Section 302 sets forth the requirements for requesting a reexamination of an issued patent. 35 U.S.C § 302 (providing in pertinent part that, "[a]ny person at any time may file a request for reexamination by the Office of any claim of a patent on the basis of any prior art cited under the provisions of section 301" and "[t]he request must set forth the pertinency and manner of applying cited prior art to every claim for which reexamination is requested"). Claims, however, may not be broadened via reexamination proceeding. 35 U.S.C. § 305 (providing "[n]o proposed amended or new claim enlarging the scope of a claim of the patent will be permitted in a reexamination proceeding").

73. A reexamined claim is enlarged "if it includes within its scope any subject matter that would not have infringed the original patent." *Thermalloy, Inc. v. Aavid Eng'g, Inc.*, 121 F.3d 691, 692 (Fed. Cir. 1997) (citations omitted). Furthermore, "[a] claim that is broader in any respect is considered to be broader than the original claims even though it may be narrower in other respects." *Quantum Corp. v. Rodime, PLC*, 65 F.3d 1577, 1580 (Fed. Cir. 1995) (citations and quotation marks omitted). "Whether amendments enlarge the scope of a claim is a matter of claim construction." *Thermalloy, Inc*, 121 F.3d at 692 (citations omitted). Invalidity is the penalty for broadening a claim during reexamination. *Quantum Corp.*, 65 F.3d at 1583–84.

H. Patent Term Extension Invalidity – 35 U.S.C. § 156

74. Section 156 provides a method by which a patentee may obtain a patent term extension for a patent, if a product which is claimed therein has undergone regulatory review prior to its first commercial marketing. 35 U.S.C. § 156.

75. Section 156(d) and its regulation 37 C.F.R. § 1.740 set forth the requirements for an application for extension of patent term. *See* Exhibit C, Paragraphs 22-24.

76. The patent term extension proceeding is not an adversarial proceeding, but an *ex parte* proceeding. There is no adversary present in the proceeding to ensure that all material information is properly before the USPTO and the HHS Secretary. As a result, the patent term extension proceeding depends significantly on the applicant presenting complete information and making accurate representations regarding the information required by Section 156.

77. Therefore, it is critical in a patent term extension proceeding that the applicant discloses material information and ensures that all representations are truthful and accurate so that the USPTO and the HHS Secretary can make proper determinations regarding the patent term.

78. Pursuant to 37 C.F.R. § 1.765, the patent owner or its agent, each attorney or agent who represents the patent owner, and "every other individual who is substantively involved on behalf of the patent owner in a patent term extension proceeding" owes "[a] duty of candor and good faith" toward the USPTO and the HHS Secretary. 37 C.F.R. § 1.765(a). Each individual owing a duty of candor and good faith, under this section, is required to bring any "material information adverse to a determination of entitlement to the extension sought, which has not been previously made of record in the patent term extension proceeding" to the attention of the USPTO or the HHS Secretary as soon as practicable. *Id.* The regulations provide that "[i]nformation is material where there is a substantial likelihood that the Office or the Secretary would consider it important in determinations to be made in the patent term extension." *Id.*

79. A patent term extension challenge may be sought in litigation where the patentee seeks to enforce a patent during the patent term extension. *See* 35 U.S.C. § 282. A party seeking to challenge a patent term extension must show by "clear and convincing evidence that the term extension was invalid." *Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284, 1291 (Fed. Cir. 2006).

V. Unenforceability Defenses

A. Inequitable Conduct

80. "Patent applicants and those substantively involved in the preparation or prosecution of a patent application owe a 'duty of candor and good faith' to the PTO." *M. Eagles Tool Warehouse, Inc. v. Fisher Tooling Co.*, 439 F.3d 1335, 1339 (Fed. Cir. 2006). These individuals have "a duty to disclose to the PTO all information known to each individual that is material to the issue of patentability." *Avid Identification Sys. v. Crystal Imp. Corp.*, 603 F.3d 967, 973 (Fed. Cir. 2010). A breach of the duty can constitute inequitable conduct, an equitable defense to patent infringement. *See Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1288 (Fed. Cir. 2011).

81. The law of inequitable conduct changed in 2011[2] with the Federal Circuit's *en banc* decision in *Therasense*. The Federal Circuit in *Therasense* considerably tightened the standards for finding inequitable conduct. *Id.* at 1290.

82. To prove inequitable conduct under the *Therasense* standard, a patent challenger must offer clear and convincing evidence that the patent applicant "misrepresented or omitted material information with the specific intent to deceive the [US]PTO." *Id.* at 1287.

83. Regarding the materiality factor, the court in *Therasense* replaced the prior "reasonable examiner" standard[3] for determining materiality in favor of a "but-for materiality" standard. *Therasense*, 649 F.3d at 1291. Under this higher standard, withheld prior art is material "if the PTO would not have allowed a claim had it been aware of the undisclosed prior art." *Id.*

84. Regarding "intent to deceive" factor under *Therasense,* a court "may infer intent from indirect and circumstantial evidence," but doing so must be "'the single most reasonable inference able to be drawn from the evidence.'" *Id.* (quoting *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 573 F.3d 1357, 1366 (Fed. Cir. 2008). "Indeed, the evidence 'must be sufficient to *require* a finding of deceitful intent in the light of all the

[2] Because *Therasense* was decided by the United States Supreme Court in 2011, after the settlement of the Namenda Litigation, I have not relied upon the case in this matter. I mention it for completeness and because a reasonable and competent patent attorney would have been aware of and followed the progress of the case when advising the parties to the Namenda Litigation.

[3] Prior to *Therasense*, the Federal Circuit had adopted the "reasonable examiner standard" under which information was material if there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the patent. *Am. Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1362 (Fed. Cir. 1984).

circumstances.'" *Id.* at 1290 (quoting *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 873 (Fed. Cir. 1988)).

85. The court in *Therasense* also replaced a "balancing test" that was used previously. Under the prior test, a greater showing of one of the above two factors would allow a lesser showing of the other. *Id.* at 1290. Under the new test, "a district court may not infer intent solely from materiality. Instead, a court must weigh the evidence of intent to deceive independent of its analysis of materiality." *Id.*

86. Accordingly, the *Therasense* standard increased the difficulty for an alleged infringer to prove inequitable conduct.

EXHIBIT N

TIMELINE

Based on Patent Term Extension Application as Filed "Start of Testing Period"

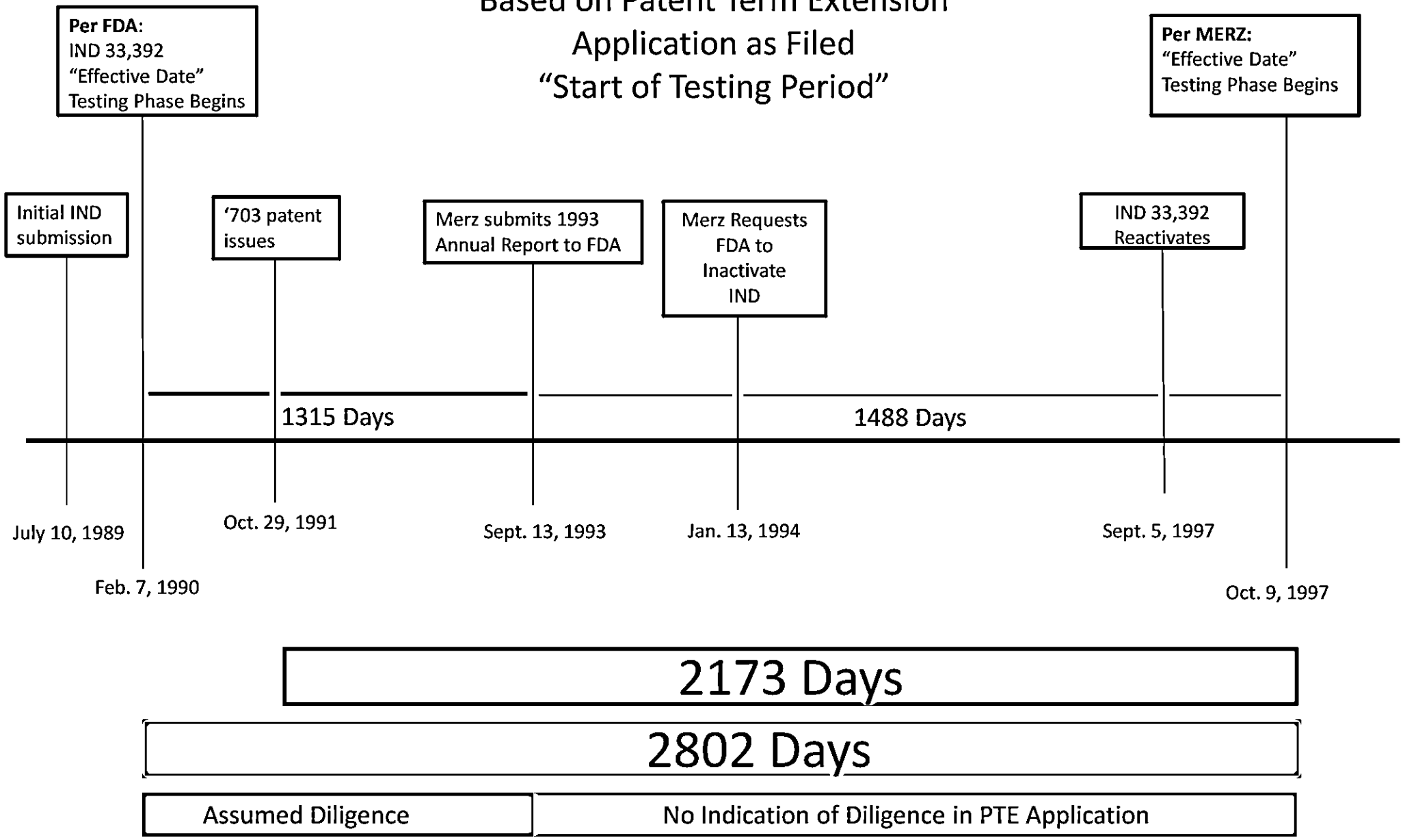


EXHIBIT O

Materials Considered and Relied Upon

1. First Amended Class Action Complaint, *JM Smith Corp. v. Actavis, PLC*, No. 15-7488 (S.D.N.Y.), ECF No. 28.

2. Manual of Patenting Examining Procedure (Eighth edition; Rev. 8 – July 2010)

3. Title 35 of the United States Code

4. Title 37 of the Code of Federal Regulations

5. Volumes 67, and 72 of the Federal Register

6. United States Constitution

7. Federal Rules of Appellate Procedure

8. United States Supreme Court Rules

9. House Report No. 98-857 (1984)

10. 130 Congressional Record (daily ed. Aug. 8, 1984)

11. The Federal Circuit Bar Association Model Patent Jury Instructions (February 2010; July 2016)

12. Northern District of California Model Patent Jury Instructions (July 2015)

13. BLACK'S LAW DICTIONARY (9th ed. 2009)

14. Merriam-Webster Dictionary

15. Namenda (memantine HCL) Package Insert

16. FDA, Drug Approval Package, Namenda (Memantine HCl) Tablets

17. FDA, Drug Approval Package, Namenda Oral Solution

18. FDA, Drugs@FDA: FDA Approved Drug Products

19. Forest's IND No. 33-392 and related correspondence (FRX-AT-00526763-869; FRX-AT-02192677-3100; FRX-AT-0237388-551; FRX-AT-02319337-688; FRX-AT-02187628-629; FRX-AT-02182331-334; FRX-AT-02178443-493; FRX-AT-02178057-8115; FRX-AT-02186837-838; FRX-AT-02178433-442; FRX-AT-02184420-421; FRX-AT-02191000-1002)

20. Forest's NDA No. 21-627 (FRX-AT-00339837-40031; FRX-AT-03080240-731; FRX-AT-03324127-661)

21. Public Pair, http://portal.uspto.gov/pair/PublicPair

    a. United States Patent No. 5,250,534

    b. United States Patent No. 6,469,012

    c. United States Patent No. 644,077

    d. United States Patent No. 5,061,703

    e. History of U.S. Patent No. 5,061,703

    f. History of U.S. Patent Application No. 90/007,176

22. EP 0392059

23. CP 2,041,453

24. Canadian Patent Office Manual of Patent Office Practice

25. Guidelines for Examination in the European Patent Office

26. Bundespatentgericht [Federal Patent Court] December 11, 2007, 3 Ni 59/05 (EU) BPatG 253 (F.R.G.) – Torrent-Memantine 00009075 – Torrent-Memantine 00009114 (English Translation) (Torrent-Memantine 00009075-9114)

27. *Lundbeck Canada Inc. v. Ratiopharm Inc.*, 2009 FC 1102 (Fed. Ct. November 23, 2009) (Can.)

28. Paragraph IV Notice Letters Regarding the '703 Patent

    a. Cobalt Labs, Inc. (FRX-AT-03490244-277)

    b. Lupin Pharma's (FRX-AT-03490110-131)

    c. TEVA Pharmaceuticals USA Inc. (FRX-AT-03488151-168)

    d. Upsher-Smith Laboratories (FRX-AT-03169274-299)

    e. Wockhardt USA (FRX-AT-03490173-243)

    f. Barr Laboratories Inc (FRX-AT-02588339-346)

    g. Dr. Reddy's Limited (FRX-AT-03490041-068)

    h. Genpharm LP (FRX-AT-03490069-109)

    i. Interpharm Inc. (FRX-AT-03490296-318)

j. Mylan Pharmaceuticals Inc. (FRX-AT-03490132-172)

k. Sun India (FRX-AT-03169490-503)

l. Synthon (FRX-AT-03169532-547)

m. Apotex (FRX-AT-03169548-561)

n. Ranbaxy Laboratories Ltd. (FRX-AT-03483932-947)

o. Orchid Healthcare (FRX-AT-03169232-273)

29. PACER – Public Access Court Electronic Court Records (https://pacer.login.uscourts.gov/csologin/login.jsf?appurl=pcl.uscourts.gov/search) Docket Entries for:

a. *Forest Labs. Inc. v. Cobalt Labs. Inc.*, No. 08-21 (D. Del.)

b. *Forest Labs. Inc. v. Barr Labs. Inc.*, No. 08-22 (D. Del.)

c. *Forest Labs. Inc. v. Dr. Reddy's Labs. Inc.*, No. 08-52 (D. Del.)

d. *Forest Labs. Inc. v. Orgenus Pharma Inc.*, No. 08-291 (D. Del.)

e. *Forest Labs. Inc. v. Apotex Inc.*, No. 08-336 (D. Del.)

f. *Forest Labs. Inc. v. Genpharm, L.P.*, No. 08-444 (E.D.N.Y.)

g. *Forest Labs. Inc. v. Kendle*, No. 08-78 (S.D. Ohio)

h. *Forest Labs. Inc. v. Lupin Pharm., Inc.*, No. 08-239 (D. Md.)

i. *Forest Labs. Inc. v. Mylan Pharma. Inc.*, No. 08-73 (N.D. W. Va.)

j. *Forest Labs. Inc. v. Sun India Pharma. Indus. Ltd.*, No. 08-749 (N.D. Ill.)

k. *Forest Labs. Inc. v. Synthon Pharma, Inc.*, No. 08-150 (E.D.N.C.)

l. *Forest Labs. Inc. v. Upsher-Smith Labs., Inc.*, No. 08-253 (D. Minn.)

m. *Forest Labs Inc. v. Orgenus Pharma Inc.*, No. 09-5105 (D.N.J.)

n. *Forest Labs. Inc. v. Aurobindo Pharma USA Inc.*, No. 14-0833 (D. Del.)

30. *Forest Labs. Inc. v. Cobalt Labs. Inc.*, No. 08-21 (D. Del)

a. Proposed Joint Pretrial Order (MNAT_0000001-301)

b. Initial Disclosures

i. Apotex (FRX-AT-03502337-345)

ii. Barr (FRX-AT-03502346-354)

iii. Cobalt (FRX-AT-03502273-279)

iv. Dr. Reddy's (FRX-AT-03502295-304)

v. Forest and Merz (FRX-AT-03502256-265)

vi. Forest and Merz 1st Supplemental (FRX-AT-03511044-1051)

vii. Genpharm (FRX-AT-03502436-445)

viii. Interpharm (FRX-AT-03502305-314)

ix. Lupin (FRX-AT-03502483-486)

x. Mylan (FRX-AT-03502414-423)

xi. Mylan 1st Supplemental (FRX-AT-03511538-546)

xii. Mylan's 2nd Supplemental (FRX-AT-03511662-669)

xiii. Orchid India (FRX-AT-03502446-452)

xiv. Orchid Pharma (FRX-AT-03502453-460)

xv. Orgenus (FRX-AT-03502395-401)

xvi. Sun (FRX-AT-03502461-471)

xvii. Teva (FRX-AT-03502503-513)

xviii. Upsher-Smith (FRX-AT-03502514-525)

xix. Wockhardt (FRX-AT-03502371-382)

c. Defendants' Requests for Production and Interrogatories

i. Defendants Collectively (FRX-AT-03503444-465; FRX-AT-03511402-408)

ii. Cobalt (FRX-AT-03502869-899)

iii. Dr. Reddy's (FRX-AT-03502944-792; FRX-AT-03508030-8036)

iv. Orchid (FRX-AT-03501587-594)

v. Orgenus (FRX-AT-03502152-160)

vi. Apotex (FRX-AT-03511332-338)

d. Plaintiffs' Requests for Production and Interrogatories

i. Collective (FRX-AT-03502908-927; FRX-AT-03503395-403)

ii. Orchid RFP (FRX-AT-03501561-571; FRX-AT-03502099-107; FRX-AT-03501554-560)

e. Defendants' Request For Production and Interrogatory Responses

i. Orchid (FRX-AT-03512475-502; FRX-AT-03508938-947; FRX-AT-03508948-957; FRX-AT-03505031-062; FRX-AT-03505016-5030)

ii. Orgenus (FRX-AT-03502207-223; FRX-AT-03502564-577)

iii. Genpharm (FRX-AT-03503648-691; FRX-AT-03509044-9055)

iv. Lupin (FRX-AT-03503743-774; FRX-AT-03505200-224)

v. Mylan (FRX-AT-03503692-734; FRX-AT-03509614-628; FRX-AT-03505162-194; FRX-AT-04228504-556)

vi. Sun (FRX-AT-03505316-353; FRX-AT-03509148-152; FRX-AT-03504901-4930)

vii. Teva (FRX-AT-03504084-137; FRX-AT-03509310-319; FRX-AT-03505354-387; FRX-AT-03521777-805)

viii. Upsher-Smith (FRX-AT-03503847-882; FRX-AT-03509115-122; FRX-AT-03504800-4831)

ix. Wockhardt (FRX-AT-03504145-182; FRX-AT-03504832-4886)

x. Amneal (FRX-AT-03509095-102)

xi. Apotex (FRX-AT-03508989-996; FRX-AT-03505120-148)

xii. Barr (FRX-AT-03509008-017; FRX-AT-03505075-106)

xiii. Cobalt (FRX-AT-03508934-937; FRX-AT-03504763-788)

xiv. Dr. Reddy's (FRX-AT-03508969-976; FRX-AT-03504943-972)

xv. Interpharm (FRX-AT-03504973-5002)

f. Plaintiffs' Request for Production and Interrogatory Responses - (FRX-AT-03513606-651; FRX-AT-03505278-313; FRX-AT-03503883-961; FRX-AT-03503962-4040; FRX-AT-03508221-229; FRX-AT-3511674-682; FRX-AT-

03504553-559; FRX-AT-03508069-076; FRX-AT-03508363-367; FRX-AT-03502550-563)

g. Requests for Admissions (FRX-AT-03501572-579; FRX-AT-03513543-584; FRX-AT-03521920-961; FRX-AT-03521610-651; FRX-AT-03511409-488)

h. Responses to Requests for Admissions (FRX-AT-03501774-786; FRX-AT-03510577-592; FRX-AT-03511683-754; FRX-AT-03521694-709

i. Plaintiffs' Privilege Log (FRX-AT-03513476-542)

j. Expert Reports and References Cited Therein

   i. Expert Report of Dr. Rachelle S. Doody

   ii. Opposition Expert Report of Rachelle S. Doody, M.D., Ph.D

   iii. Opposition Expert Report of Martin R. Farlow, M.D.

   iv. Opposition Expert Report of Roberto Malinow, M.D., Ph.D

   v. Supplemental Expert Report of Roberto Malinow, M.D., Ph.D

   vi. Opposition Expert Report of Christopher A. Lipinski, Ph.D.

   vii. Expert Report of John P. Murry, Jr., Ph.D

   viii. Expert Report of Cameron K. Weiffenbach

   ix. Expert Report of Harry C. Boghigian

   x. Expert Report of Jerry Joseph Buccafusco, Ph.D

   xi. Expert Report of Paul Spencer Fishman, M.D., Ph.D

   xii. Rebuttal Expert Report of John Olney, M.D.

   xiii. Expert Report of David A. Greenberg, M.D. Ph.D

k. Deposition Transcripts

   i. Joachim Bormann, May 30, 2009

   ii. David A. Greenberg, Feb. 18, 2010

   iii. Roberto Malinow, M.D. Ph.D., Jan. 26, 2010

   iv. Rachelle Doody, M.D., Feb. 19, 2010

v. Martin R. Farlow, M.D., Jan. 18, 2010

vi. Paul S. Fishman, M.D., Ph.D., Jan. 20, 2010

vii. Roman Gortelmeyer, Oct. 29, 2009

viii. Walter Wolfgang Fleischhacker, M.D., Sept. 9, 2009

ix. G. Patrick Sage, July 29, 2009

x. Christopher Andrew Lipinski, Feb. 17, 2010

xi. Harry C. Bohigian, Jan. 15, 2010

xii. Howard Fillit, M.D., June 9, 2009

xiii. Jerry Joseph Buccafusco, Jan. 19, 2010

xiv. John Olney, M.D., Jan. 29, 2010

xv. Myron Weiner, M.D., May 13, 2009

xvi. John P. Murry, Jr., Ph.D., Jan. 22, 2010

xvii. Adda Gogoris, July 14, 2009

l. Invoices (FRX-AT-03521981-987; FRX-AT-03522157-159; FRX-AT-03522163; FRX-AT-03522170; FRX-AT-03522161; FRX-AT-03522160; FRX-AT-03522166; FRX-AT-03522165; FRX-AT-03522162; FRX-AT-03522164; FRX-AT-03522167-169; FRX-AT-03522171-174; FRX-AT-03521988-2007; FRX-AT-03522336-338; FRX-AT-03521978-980; FRX-AT-03522184-191; FRX-AT-03522355-356; FRX-AT-03522350-354; FRX-AT-03522157-159; FRX-AT-03522124-127; FRX-AT-03522128-132; FRX-AT-03522133-137; FRX-AT-03522365-367; FRX-AT-03522371-373; FRX-AT-03522138-140; FRX-AT-03522141-143; FRX-AT-03522368-370; FRX-AT-03522150-152)

m. Namenda Litigation Settlement Agreements

i. Dr. Reddy's (FRX-AT-00000001-037)

ii. Cobalt (FRX-AT-00000038-061)

iii. Sun (FRX-AT-00000112-147)

iv. Upsher-Smith (FRX-AT-00000148-183)

v. Teva (FRX-AT-00000184-217)

vi. Amneal (FRX-AT-00000218-252)

vii. Apotex (FRX-AT-00000274-298)

viii. Lupin (FRX-AT-00000340-362)

ix. Orgenus and Orchid (FRX-AT-00000380-402)

x. Wockhardt (FRX-AT-01710237-272)

xi. Mylan (FRX-AT-00000428-463)

31. Paul M. Janicke & LiLan Ren, *Who Wins Patent Infringement Cases?* 34:1 AIPLA Quarterly Journal, 1–43 (2006).

32. Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration: An FTC Study* (July 2002).

33. Adam Greene & D. Dewey *Steadman, Pharmaceuticals: Analyzing Litigation Success Rates*, RBC Capital Markets Industry Comment (January 2010).

34. U.S. Dep't for Health & Human Servs., Ctrs. for Disease Control & Prevention, Anthropometric Reference Data for Children & Adults: United States, (2011-2014)

35. J. Benjamin Bai, *Enablement Issues Concerning Aggressively Broad Generic Claims*, 7 Nw. J. of Tech. & Intellectual Property, (Fall 2008).

36. United States Court of Appeals for the Federal Circuit, *Median Time to Disposition of Cases Terminated After Hearing or Submission*, (FY 2007–2016)

37. *The Statistics*, 126 Harv. L. Rev. 388 (2012)

38. *The Statistics*, 127 Harv. L. Rev. 408 (2013)

39. *The Statistics*, 128 Harv. L. Rev. 401 (2014)

40. *A Reporter's Guide to Applications Pending Before the Supreme Court of the United States*, https://www.supremecourt.gov/publicinfo/reportersguide.pdf (last accessed August 29, 2017.

41. *Report of the Economic Survey*, AIPLA, (2009)

42. *Report of the Economic Survey*, AIPLA, (2011)

43. Kirkland Estimate (FRX-AT-04248512-513)

44. Feb. 18, 2010 "Standstill" Letter Agreement (FRX-AT-03629655-656)

45. Draft Anti-Trust Complaint (FRX-AT-0329662-683)

46. R. Vacca, *Acting Like an Administrative Agency: The Federal Circuit En Banc*, 76 Mo. L. Rev. 733, 736 (2011)

47. C. Cotropia, *Determining Uniformity within the Federal Circuit by Measuring Dissent and En Banc Review*, 43 Loy. L.A. L. Rev. 801, 817 (2010)

Considered to the extent set forth in the Report

48. C. Scott Hemphill & Mark A. Lemley, *Earning Exclusivity: Generic Drug Incentives and the Hatch-Waxman Act*, 77:3 Antitrust Journal, 947–89 (2011)

49. Mark A. Lemley, *Where to File Your Patent Case*, 38:4 AIPLA Quarterly Journal Pages 1–37 (Fall 2010)

50. PricewaterhouseCoopers, *Patent Litigation Study: Big cases make headlines, while patent cases proliferate* (2013)